A.M.A.

Archives OF NEUROLOGY AND PSYCHIATRY

NOVEMBER 1956

VOLUME 76 NUMBER 5

AMERICAN MEDICAL ASSOCIATION Publication

COLONIAL HALL

One of Fourteen units in "Cottage Plan"

For Nervous Disorders

Maintaining the highest standards since 1884, the Milwaukee Sanitarium Foundation continues to stand for all that is best in the contemporary care and treatment of nervous disorders.

Photographs and particulars sent on request.

Josef A. Kindwall, M.D.
Carroll W. Osgood, M.D.
William T. Kradwell, M.D.
Benjamin A. Ruskin, M.D.
Lewis Danziger, M.D.
James A. Alston, M.D.
Edward C. Schmidt, M.D.
Isaac J. Sarfatty, M.D.

★

Waldo W. Buss, Executive Director

Chicago Office—1509 Marshall Field Annex Bldg.
25 East Washington St.—Wednesday, 1-3 P.M.
Phone—Central 6-1162

MILWAUKEE SANITARIUM FOUNDATION, INC.

Wauwatosa Wisconsin

TABLE OF CONTENTS

VOLUME 76 NOVEMBER 1956 NUMBER 5

ORIGINAL ARTICLES

SECTION ON NEUROLOGY

OBITUARIES

REGULAR DEPARTMENTS

SECTION ON PSYCHIATRY

REGULAR DEPARTMENTS

A. M. A.
Archives of Neurology and Psychiatry

VOLUME 76 NOVEMBER 1956 NUMBER 5

Published monthly by the AMERICAN MEDICAL ASSOCIATION. Editorial and Circulation Offices: 535 North Dearborn Street, Chicago 10, Illinois. Publication Office: Thompson Lane, Box 539, Nashville 1, Tennessee. Change of Address: Notice to the circulation office should state whether or not change is permanent and should include the old address. Six weeks' notice is required to effect a change of address. Second-class mail privileges authorized at Nashville, Tenn., Aug. 6, 1956.

Instructions to Contributors

Communications regarding editorial management, subscriptions, reprints, etc., should be addressed to Specialty Journals, American Medical Association, 535 North Dearborn Street, Chicago 10.

Articles, book reviews, and other materials for publication should be addressed to the Chief Editor of the Specialty Journal concerned. Articles are accepted for publication on condition that they are contributed solely to that journal.

An original typescript of an article should be provided; it must be double or triple spaced on one side of a standard size page, with at least a 1-inch margin at each edge. A carbon copy should be retained by the author. An article in English by a foreign author should be accompanied by a draft in the author's mother tongue. Improvised abbreviations should be avoided.

The main title of an article may not contain more than seventy characters and spaces; a subtitle may be of any length. The subtitle should be sufficiently detached from the main title that a punctuation mark as strong as a colon can be used in the Table of Contents to separate it from the main title; it must not begin with "with."

The author's name should be accompanied by the highest academic or medical degree which he holds. If academic connections are given for one author of an article, such connections must be given for all other authors of the article who have such connections.

A Case Report must be preceded by an introductory paragraph containing at least thirty words before the details of the case are given. To avert the possibility of legal action, patients' initials and hospital case numbers should not be published.

Material quoted from another publication must be quoted exactly if the original is in English—spelling, capitalization, punctuation, etc., unchanged. Material taken largely from another publication must be credited to the original author, whether quoted exactly or merely abstracted.

Each article should be accompanied by a summary in the present tense, presenting the main points of the article, but in somewhat more generalized terms than in the article itself.

If it is necessary to publish a recognizable photograph of a person, the photograph must be accompanied by written permission of the subject himself if an adult, or of the parents or guardian if a child, to publish his photograph. An illustration which has been published in another publication must be accompanied by written permission from the author and the original publisher to reproduce it in an A. M. A. Specialty Journal.

The maximum illustration allowance is ten illustrations within a total of 100 sq. inches or $100, whichever is of greater advantage to the author. When no restrictions are placed by the author upon cropping, reducing, and grouping, the publisher is often able to use twenty or more illustrations in one article with the $100 allowance. See an issue of this journal for examples. Oversized originals should be photographed and a print submitted. Large photomicrograph prints will be reduced in scale unless portions to be cropped are indicated by the author.

Any cut-off marks should be made on the margins (or mountings) rather than on the illustration itself. Charts and drawings should be in black ink on hard, white paper. Lettering must be large enough to permit necessary reduction. Glossy prints of x-rays are requested. Paper clips should not be used on prints, since their mark shows in reproduction, as does writing on the back of prints with hard lead pencil or stiff pen. Labels should be prepared and pasted to the back of each illustration showing its number, the author's name, an abbreviated title of the article, and top plainly indicated. Charts and illustrations must have descriptive legends, grouped on a separate sheet. Tables must have captions. ILLUSTRATIONS SHOULD BE UNMOUNTED.

References to the literature should be numbered in the order in which they are referred to in the text or listed in alphabetical order without numbers. A chronological arrangement, with all entries for a given year alphabetized according to the surname of the first author, may be used if preferred. References should be typed on a special page at end of manuscript. They should conform to the style of the Quarterly Cumulative Index Medicus, and must include, in the order given, name of author, title of article (with subtitle), name of periodical, with volume, page, month—day of month if weekly or biweekly—and year. Names of periodicals should be given in full or abbreviated exactly as in the Quarterly Cumulative Index Medicus. Reference to books must contain, in the order given, name of author, title of book, city of publication, name of publisher, and year of publication. Titles of foreign articles, if originally in a generally known Romance or Germanic tongue, must either all be in English translation or all be in the original language. Titles in other languages must be translated. The author must assume responsibility for the accuracy of foreign titles.

AMERICAN MEDICAL ASSOCIATION

535 North Dearborn Street **Chicago 10**

INDEX TO
NEUROPSYCHIATRIC INSTITUTIONS SPECIAL SCHOOLS and SANITARIA
Advertising in
A.M.A. Archives of NEUROLOGY and PSYCHIATRY

Display announcements of the following institutions appear regularly in A. M. A. Archives of NEUROLOGY and PSYCHIATRY. For advertisements of those institutions which run on an *every-other* month basis it would be necessary to consult the advertising section of a previous or *subsequent issue*.

ADAMS HOUSE ..... **Boston, Jamaica Plain, Mass.**
James Martin Woodall, M.D., Medical Director

APPALACHIAN HALL ..... **Asheville, N. C.**
Wm. Ray Griffin, M.D.

BALDPATE ..... **Georgetown, Mass.**
G. M. Schlomer, M.D.

BEVERLY FARM, INC. ..... **Godfrey, Ill.**
Dr. Groves B. Smith, Superintendent

FAIRVIEW SANITARIUM ..... **Chicago, Ill.**
Dr. J. Dennis Freund, Medical Director

HALL-BROOKE ..... **Greens Farms, Conn.**
Dr. Geo. S. Hughes, Medical Director

LIVERMORE SANITARIUM ..... **Livermore, Calif.**
O. B. Jensen, M.D., Superintendent and Medical Director

MENNINGER FOUNDATION ..... **Topeka, Kan.**
J. Cotter Hirschberg, M.D., Director

MILWAUKEE SANITARIUM FOUNDATION, INC. ..... **Wauwatosa, Wis.**

NORTH SHORE HEALTH RESORT ..... **Winnetka, Ill.**
Samuel Liebman, M.D., Medical Director

MARY POGUE SCHOOL, INC. ..... **Wheaton, Ill.**
Barclay J. MacGregor, Manager and Registrar

THE RING SANATORIUM ..... **Arlington, Mass.**
Benjamin Simon, M.D., Director

RIVER CREST SANITARIUM ..... **Astoria, Queensboro, N. Y. City**
and BELLE MEAD FARM COLONY ..... **Belle Mead, N. J.**
Dr. J. J. Kindred, Founder and Consultant

INFLUENCING THE SAFETY

OF ELECTROCONVULSIVE THERAPY

'ANECTINE'®

CHLORIDE brand
SUCCINYLCHOLINE CHLORIDE

"...removes practically all of the previous risks inherent in the treatment."[1]

respiratory safety

"...patients treated with this muscle relaxant, though often apneic, are readily ventilated with oxygen. Skin color remains excellent."[2]

"The most important [observation] is the elimination of hypoxia or anoxia."[3]

cardiovascular safety

"The arterial blood pressure is found to rise during the [unmodified] electroshock. When the muscular spasms and the asphyxia are eliminated with the administration of succinylcholine and oxygen, a slower and more even rise is noted; . . ."[4]

"In ordinary electroshock therapy the heart rate is found to be irregular and greatly increased. Muscular relaxation produced by succinylcholine is noted to result in a slower and more even rate."[4]

orthopedic safety

"... the occurrence of fractures and dislocations has been reduced to zero."[3]

"No fractures occurred in the group during therapy."[5]

over-all safety

"Modification of electro-convulsive therapy with thiopental sodium and succinylcholine chloride is a much safer treatment as shown by the absence of fractures and medical complications in our series of 7,500 treatments."[1]

references:

1. Saltzman, C., Konikov, W., and Relyea, R. P.: Dis. Nerv. System 16:*155, 1955. 2. Nowill, W. K., Wilson, W., and Borders, R.: A.M.A. Arch. Neurol. & Psychiat.* 71:*189, 1954. 3. Steven, R. J. M., Tovell, R. M., Johnson, J. C., and Delgado, E.: Anesthesiology* 15:*623, 1954. 4. Holmberg, G., et al.: A.M.A. Arch. Neurol. & Psychiat.* 72:*73, 1954. 5. Wilson, W. P., and Nowill, W. K.: ibid.* 71:*122, 1954.*

'ANECTINE' Chloride brand Succinylcholine Chloride INJECTION *For intravenous injection*
20 mg. per cc.
Multi-dose vials of 10 cc.

'B.W.& CO.' A MARK TO REMEMBER

BURROUGHS WELLCOME & CO. (U. S. A.) INC., Tuckahoe, New York

relaxes both the body and the mind

well suited for prolonged therapy

- well tolerated, nonaddictive, essentially nontoxic
- no blood dyscrasias, liver toxicity, Parkinson-like syndrome or nasal stuffiness
- chemically unrelated to chlorpromazine or reserpine
- does not produce significant depression
- orally effective within 30 minutes for a period of 6 hours

Indications: **anxiety and tension states, muscle spasm.**

THE ORIGINAL MEPROBAMATE

Miltown®

Tranquilizer with muscle-relaxant action

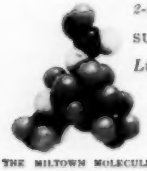
DISCOVERED AND INTRODUCED

BY WALLACE LABORATORIES, *New Brunswick, N.J.*

2-methyl-2-n-propyl-1,3-propanediol dicarbamate—U.S. Patent 2,724,720

SUPPLIED: *400 mg. scored tablets. Usual dose: 1 or 2 tablets t.i.d.*

Literature and Samples Available on Request



THE MILTOWN MOLECULE

CM 3708-R

Section on NEUROLOGY

Ultrasonically Produced Changes in the Blood-Brain Barrier

L. BAKAY, M.D.
T. F. HUETER, Ph.D.
H. T. BALLANTINE JR., M.D.
and
D. SOSA, M.D., Boston

It has been demonstrated in recent years * that focused ultrasound of frequencies ranging from 0.9 to 2.5 megacycles (mc), and at intensities of from 200 to 1500 watts per square centimeter, may be used to produce circumscribed small lesions in the central nervous system. Histological examination of the tissue damaged by focused ultrasound does not reveal the mechanism of destruction, although the morphological appearance of ultrasonic lesions differs specifically from other types of lesions.[2]

A cardinal point in understanding the effect of ultrasound on central nervous tissue is knowledge of the reaction of the cerebral capillaries to this type of injury. Both the absence of gross hemorrhage and the existence of edema have been reported by some investigators.† Thus, the extent of capillary damage and its possible role in the development of a lesion are important from the point of view of the physiological effect of ultrasound. For this reason a general investigation of the changes in the blood-brain barrier produced by focused ultrasound has been undertaken.

Ultrasonic Irradiation Technique

In the work to be reported here, focused ultrasound of a frequency of 2.5 mc. is applied by stereotactic procedures[8] to specific sites within the cat brain. A detailed account of the physical and biological aspects of this method has been given elsewhere.‡

The schematic diagram of Figure 1 illustrates the manner in which the focused ultrasonic beam is applied to the brain of a cat, whose head is fixed in a standard Horsley-Clark holder.

A portion of the skull is removed at the port of entry of the converging ultrasonic beam to eliminate beam distortion and absorption caused by bone. The dura, however, need not be opened. Since the passage of ultrasound is effectively blocked by even the thinnest layer of air, a "coupling pan" filled with degassed saline is attached with its lower rim to the scalp of the animal. Figure 1 also shows in a schematic fashion the use of stereotactic coordinates, the letter L representing lateral displacement from the midline, the letter H representing vertical displacement above the zero plane of the coordinate system. In the Jasper-Marson stereotactic "Atlas" used by us, the coordinate zero plane is located 10 mm. above the plane passing through the ear-bar

Received for publication April 27, 1956.

From the Department of Neurosurgery, Massachusetts General Hospital.

This work was supported by a research grant (DA-49-007-ND-523) from the Department of the Army, Office of the Surgeon General, and in part by a research grant (B212-C 3) from the National Institute of Neurological Diseases and Blindness, National Institutes of Health, U. S. Public Health Service.

* References 6, 7.

† References 2, 3.

‡ Ballantine, H. T.; Hueter, T. F.; Nauta, W. J. H., and Sosa, D.: Focal Destruction of Nervous Tissue by Focused Ultrasound: Biophysical Factors Influencing Its Application, to be published. Hueter, Ballantine, and Cotter.[7]

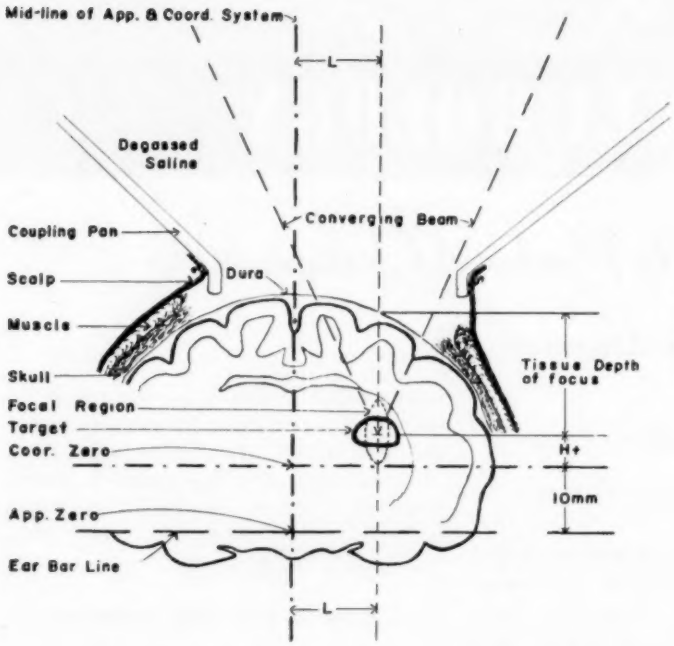


Fig. 1.—Schematic drawing of stereotactic irradiation procedure used in the production of focused ultrasonic lesions in the cat brain.

line. The ultrasonic applicator, consisting of a piezoelectric quartz plate and a polystyrene lens, is positioned by external mechanical coordinates, as shown in Figure 2, such that the center of the ellipsoidal focal region of highest sound intensity coincides with the coordinates of the particular brain structure to be affected. In most cases the target has been subjected to pulsed irradiation to allow for dissipation of the ultrasonically produced heat. The results discussed in this paper have been observed with ultrasonic doses of about 30 to 50 pulses of 0.4 second's duration, administered at the rate of one per second and at a focal intensity of approximately 600 watts per square centimeter.

Tracer Methods

A standard dose of 0.5 mc. of P^{32} was injected intravenously, 10 minutes to 5 days after ultrasonic irradiation. A trypan blue solution, containing 0.1 gm. of the dye per kilogram of body weight in 0.45% NaCl, was injected into a leg vein 5 to 45 minutes after administration of the isotope. Five to fifteen minutes after the injection of the vital dye the arterial system of the cat was perfused with 90-200 cc. of isotonic saline through the aorta. Such a rinsing is necessary in experiments of short duration to remove trypan blue from the cerebral blood vessels. The perfusion does not affect the dye deposited in a cerebral lesion. After the saline perfusion, the brain proper was also perfused with a 10% formalin solution through both carotid arteries. Control experiments have indicated that this rapid perfusion does not change the deposition pattern of radioactive phosphate in the brain and does not remove the tracer from the cerebral tissue.

The dosage factors must be carefully controlled in comparing the effect of the blood-brain barrier on vital dyes and isotopes. We have followed Broman's technique[6] in using trypan blue. A minimal dose of 0.1 gm. per kilogram of body weight was prepared fresh before injection in 0.45% NaCl, amounting to about 10-15 cc. of solution. This was boiled and filtered to avoid formation of microcrystals. Following intravenous injection the solution was left to circulate for 10-15 minutes before the cat was killed. Satisfactory concentrations of the dye in the blood vessels could be checked on the removed brain: There was distinct vital staining of the dura, hypophysis, choroid plexuses, and area postrema, while the brain proper remained unstained after saline perfusion.

Equally important is the dosage of radioactive phosphate. It is necessary to inject a dose of relatively high radioactivity, especially in experiments of short duration, because it is known that only a small fraction of the dose administered will be taken up by the brain (less than 0.1%).[3] On the other hand, it is necessary to obtain a

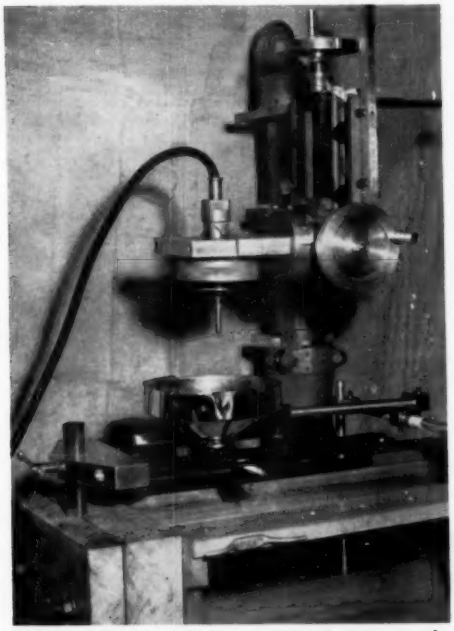


Fig. 2.—View of devices used in the stereotactic ultrasonic irradiation of cat brains. Center: ultrasonic applicator with cable leading to radiofrequency generator and with removable pointer indicating the position of the focal point. Upper right: mechanical coordinate system for positioning of applicator. Below center: open pan for coupling liquid to provide sound conduction between applicator lens and brain. Bottom: stereotactic head holder.

sufficiently high cerebral isotope concentration in order to minimize the error in determining the P^{32} content in tissue samples. We have found 0.5 mc. an adequate and convenient dose in short experiments. Naturally, the amount of this buffered solution of P^{32} must be small (0.5 to 2.0 cc.) and carrier-free to avoid interference with the amount of circulating plasma, its osmotic properties, and its total phosphate content.

Blood samples for P^{32} determination were taken before the start of the trypan blue injection. A second blood sample was taken just before perfusion.

The main purpose of the trypan blue injection was to show the exact location and extent of the lesion. The vital dye serves as a secondary tracer to facilitate the localization of P^{32}, the primary tracer, which is invisible in the gross specimen. This was particularly important in deeply situated small lesions. When not colored, such small lesions are invisible to the naked eye and can be revealed only in serial microscopic sections; however, by that time they are of no value for P^{32} determination, for several reasons. One reason is that significant amounts of the tracer are washed out of the sections during routine histological preparation. Another is the considerable decay of radioactivity during the time needed for procuring of the sections.

Occasionally the lesion, even when stained with trypan blue, was so small that it escaped direct detection if it fell accidentally between two transverse cuts of the brain, which were placed 1 to 2 mm. apart. It could still be detected by transilluminating the brain sections; since a thin section of fresh brain is quite transparent to light, the vitally stained lesion shows up as a well-defined dark spot.

In most cases the brain was cut transversally through the lesion, and one-half the specimen was fixed in 10% formalin and examined histologically with cell and myelin stains, while the other half was stored under —20 C and used for P^{32} determination. Colored photographs were prepared from each specimen, using a Kodak Close-Up apparatus with Kodachrome A Film. Black and white pictures were also made of most of the specimens for illustrative purposes and to serve as photographic control of the radioautographs.§

The P^{32} content of various portions of the brain was determined by radioautography and by direct tissue counting. Serial cross sections of the brain, including those containing the lesion, 0.5-1.0 mm. in thickness, were placed on Kodak No-Screen X-Ray Films. The films were developed in 48 to 76 hours. The sections were then cut into pieces according to the density differences of these contact radioautographs. The pieces were weighed on aluminum planchets, dried, and counted for radioactivity by scalers. The final values were expressed in counts per milligram of wet tissue per minute. For comparative purposes the tissue counts of different experiments were calculated to a standard plasma P^{32} level.

For finer details microradioautographs were prepared using the contact method described above, but with thin sections (50μ-100μ). The exposure time of these autographs varied from 7 to 14 days.

Microscopic examination of trypan blue deposition was carried out on frozen unstained sections of 20μ, 50μ, 100μ, and 200μ thickness, mounted on glass, and covered with Kayser jelly.

Experimental Results

Trypan Blue.—None of the ultrasonic lesions produced in this series of experi-

§ It was found difficult to reproduce the blue staining of lesions on black and white, even when they were colored quite brilliantly. This could be done only by using orange filters and prolonged exposure time, but even the best results could be classified only as moderately adequate.

ments failed to stain vitally with trypan blue. The brilliant blue coloration of the injured area formed a sharp contrast with the rest of the brain, which showed no trace of coloration after the perfusion of its blood vessels. The vital staining of the lesion occurred almost immediately after irradiation, certainly within a few minutes, and was therefore the only means by which small lesions could be identified at an early

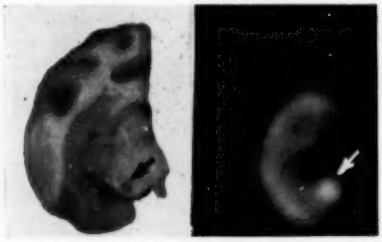


Fig. 3 (Cat 41).—Small, round ultrasonic lesion in the midbrain, three days after irradiation, vitally stained with trypan blue (left). Corresponding radioautograph (right) showing high P^{32} concentration in the lesion and in the choroid plexus of the lateral ventricle.

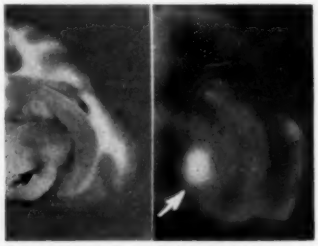


Fig. 4 (Cat 71).—Left: small ultrasonic lesion three hours after irradiation, placed caudal to the lateral geniculate body and stained with trypan blue. Right: Corresponding radioautograph revealing maximum P^{32} deposit in the lesion.

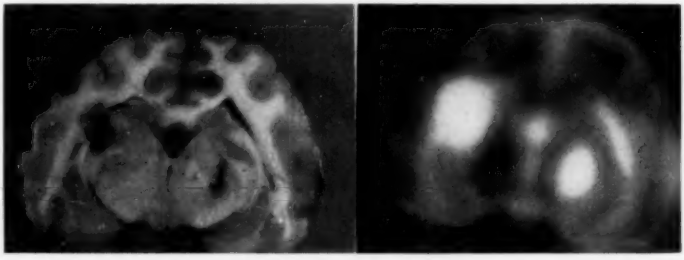


Fig. 5 (Cat 70).—Bilateral medium-sized, spindle-shaped ultrasonic lesions in and below the lateral geniculate bodies, three hours after irradiation. Left: vitally stained specmen; right: corresponding radioautograph.

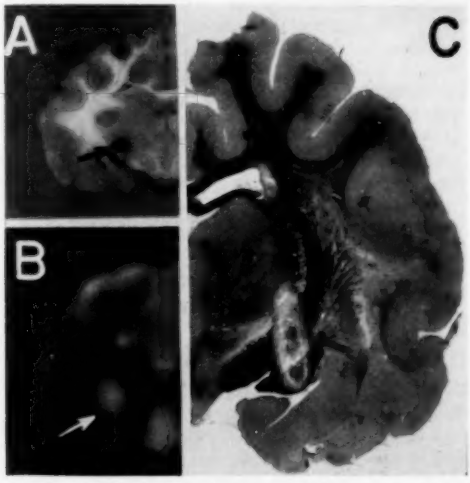


Fig. 6 (Cat 44).—Ultrasonic lesion of one day's duration, showing the "island-and-moat" pattern. *A*, vital staining with trypan blue; *B*, corresponding radioautograph; *C*, myelin-stained microscopic section.

stage, as the injured tissue did not show any other visible evidence of damage when not stained. Barnard, Fry, and associates [3] have called attention to the fact that no histological change is observed in the irradiated animal killed within five to nine minutes after exposure. They found the first evidence of tissue injury in the white matter 15 minutes after irradiation. Small lesions (less than a millimeter in diameter) were round and discrete in our preparations and showed uniform staining with trypan blue (Figs. 3 and 4). Larger ones, while still homogeneous, were apt to be somewhat spindle-shaped, their longer axis being parallel to the axis of the ultrasonic beam (Fig. 5). Large lesions showed the characteristic "island-and-moat" pattern, described by Barnard, Fry, and associates.[3] A typical lesion of this kind produced by us is shown in Figure 6. The island itself stained faintly

with the vital dye or was quite void of stain, while the moat was strongly colored, forming a dark-blue ring in the specimen.

The pattern of trypan-blue staining of any ultrasonic lesion depends on the extent of tissue destruction. The lesion area does not seem to change in size during the first few days after irradiation. There is evidence of an additional zone of edema, showing faint blue discoloration during the first hours. This effect, however, seems to be reversible and subsides with the regression of edema.

The elapsed time between trypan blue injection and death seemed to have little bearing on the intensity and size of the vitally colored area, according to our observations, which ranged from five minutes to six hours.

Radioactive Phosphate. — Radioactive phosphate concentrated heavily in the damaged area shortly after intravenous injection of the isotope. Although this accumulation of P^{32} in the injured tissue was not less remarkable than that of trypan blue, as can be seen in the radioautographs, it formed a quantitative rather than qualitative contrast with the normal brain. There was some P^{32} uptake by the uninjured brain immediately after administration of the tracer, especially along the superficial layers of the cortex and ventricular lining, but this was quite insignificant compared with the large amounts deposited in the lesion. Indeed, the only part of the brain in the vicinity of the lesions which contained similar amounts were the choroid plexuses, which are not protected by any particular barrier and amass large amounts of P^{32} from the circulating blood through their vast capillary network.

Small and medium-sized lesions were rather homogeneously saturated with radioactive phosphate (Figs. 3, 4, 5, and 6), but in large lesions the island-and-moat pattern materialized: relatively small concentrations in the island and massive deposition in the moat.

The accompanying Table shows the P^{32} content of ultrasonic lesions at various intervals after irradiation. The plasma concentration diminishes with the lapse of time from the injection of P^{32}. The concentration of the isotope in the cerebral cortex shows little variation from one to three hours after injection. However, the P^{32} concentration of the irradiated area definitely follows the decline of plasma concentration with time. Consequently, the ratio between the P^{32} content of the lesion and that of the normal cortex diminishes from 15:1, in the first hour, to 5:1 to 6:1, at the end of the second hour, and to 3:1, at the end of the third hour. This indicates that there is a linear relationship between the P^{32} concentration of the irradiated area and that of the plasma, while, on the other hand, no such

P^{32} Content of Various Parts of Central Nervous System*

Cat	Time from U. S. Radiation to Death	Time from P^{32} Injection to Death, Min.	Plasma	Cerebral Cortex	Lesion
76	1 hr.	50	46.0	2.3	33.8
71	3 hr.	105	26.0	4.0	22.6
67	3 hr.	120	11.5	4.2	23.7
49	1 day	105	2.8	2.8	6.7
47	1 day	140	5.8	5.1	14.0
44	1 day	150	9.8	3.8	8.9
36	1 day	180	5.5	3.0	7.5
39	1 day	200	5.8	3.6	10.1
41	3 days	160	10.0	3.1	7.7

* Values are expressed in counts per minute per milligram of tissues.

relation exists between normal brain and plasma.

Comparison of the Tracers.—The fundamental similarity between the two tracers, trypan blue and P^{32}, was their unfailing concentration in the area of the lesion. We were not able to find a single instance which would have revealed absence of deposition or concentration in the area of damage of only one of the two agents. The island-and-moat pattern of larger lesions was characteristic for both tracers, although much more pronounced when studied with trypan blue. Four or five days after a large ultrasonic lesion is produced, trypan blue stains only a thin margin; most of the lesion remains unstained. At the same time P^{32} concentration is still heavy in the entire lesion, although the center contains only about 50% of the isotope, as compared with the marginal zone.

The lesion as outlined with P^{32} in radioautographs was consistently larger than was the blue staining of the area (Fig. 5). This may indicate that the barrier damage when studied with a smaller-particle-sized tracer (P^{32}) is more extensive than it is when outlined with larger-particle-sized trypan blue. The difficulty which arises in comparing the two methods with absolute accuracy will be discussed below.

Tissue Resistance.—We found clear evidence that some tissues of the central nervous system are more resistant to damage than others, thus confirming the results of other investigations. Particularly damage-resistant was the gray matter, both cortical and nuclear, such, for instance, as the lateral geniculate body and other midbrain ganglia. Large ultrasonic doses administered to the internal capsule or other parts of the centrum semiovale demonstrated the large differences in susceptibility among various types of tissues. At early stages after irradiation all white matter of the involved region was stained blue, but this coloration stopped sharply at the innermost layers of the cortex or thalamus. A lesion of this kind is shown in Figure 7.

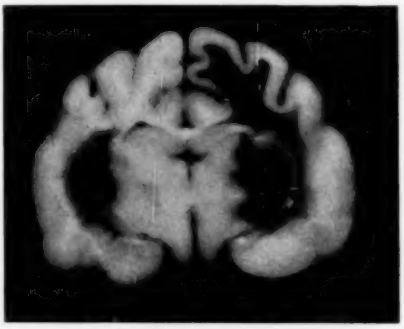


Fig. 7 (Cat 52).—Large bilateral ultrasonic lesions outlined by vital coloration with trypan blue. Note the selective damage of white matter in one of the hemispheres.

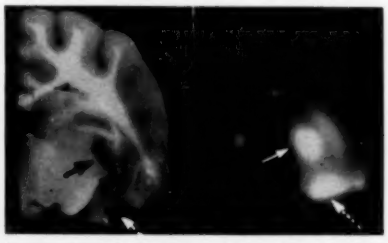


Fig. 8 (Cat 39).—Small ultrasonic lesion (Solid arrow) in the medial geniculate body and corresponding radioautograph. Dotted arrow points to the "echo lesion."

Echo Lesions.—Occasionally a second lesion could be detected at the base of the brain, visible on the surface of the ventral aspect of the temporal lobe (Fig. 8). These "echo lesions" are likely to occur whenever the diverging beam beyond the focus encounters concave regions of the base of the skull, and when a heavy dosage factor is employed, evidenced by a large-sized lesion. They may be avoided by angulated irradiation and by the choice of a dosage just sufficient to reproduce a small lesion. On coronal sections they were cone-shaped, with their wide base situated over the base of the skull. When they were small, they were stained uniformly blue; but when they were large, the blue was confined to the fringes of the lesion.

Microscopic Picture of Vitally Stained Ultrasonic Lesions.—Larger lesions, with a diameter of more than 2 mm., frequently

show a characteristic island-and-moat pattern. On gross inspection the center of such a lesion may look fairly intact and show little or no vital staining, while the moat as round, uniformly vital-stained areas. On microscopic examination of unstained frozen sections the following observations have been made (Fig. 9):

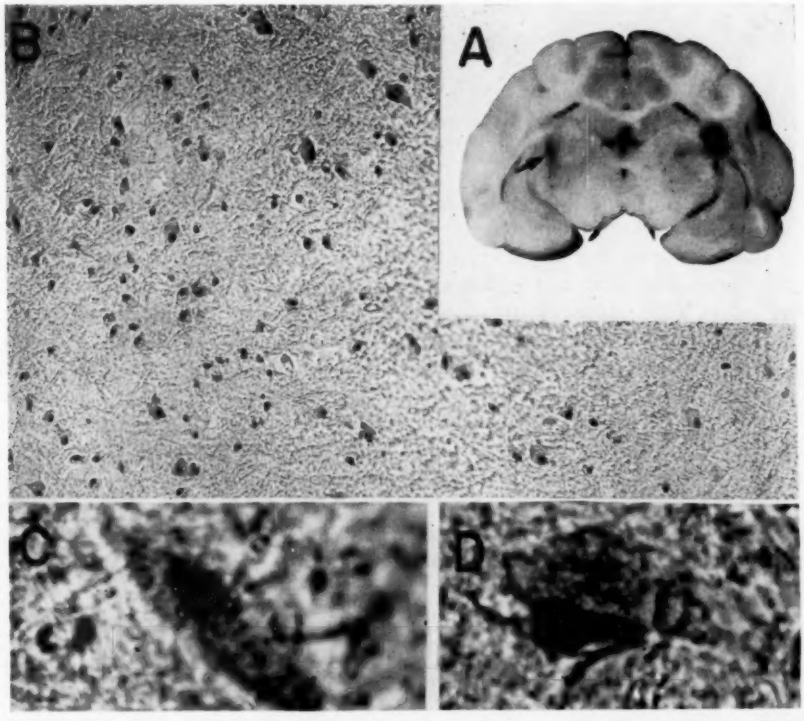


Fig. 9 (Cat 75).—*A*, bilateral vitally stained ultrasonic lesions, 30 minutes after irradiation. Arrow points to the lesion placed in the lateral geniculate body. *B*, microscopic picture of the same region. Only vital coloration with trypan blue used. *C* and *D*, enlarged view of two vitally stained nerve cells, revealing severe damage.

which surrounds the island in a ring-like fashion shows severe tissue destruction and stains intensely with trypan blue. In myelin-stained slides one can see that strands of myelin sheaths are stained and easily detected within the island. In the surrounding moat the tissue destruction is complete.

Small, distinct ultrasonic lesions in the fringe area between gray and white matter are more suitable for study of alterations in the blood-brain barrier because the damage is not so severe and widespread and can be observed more easily. Such lesions are not more than 1 or 1.5 mm. in diameter and can be detected in the gross specimen

The injured area is fairly sharply outlined, and the entire lesion shows a faint blue staining with trypan blue, which is quite diffuse and involves the entire tissue. This can be seen only by a small magnification because the very light blue discoloration is not visible under strong transillumination and high magnification. Out of this light-blue background the nerve cells stand out very markedly, owing to their intense staining with trypan blue, which is much stronger than that of other tissue elements. The nerve cells show, in addition to this diffuse staining, morphological evidence of acute damage. They vary greatly in size

and form a marked contrast with the nerve cells lying near by, but outside the boundaries of the lesion. These normal neurons show no evidence of damage; neither are they stained with trypan blue. The nuclei of the damaged neurons are small, dark, and pyknotic, and their nucleolus is all but invisible. The nucleus is displaced from its central position to the edge of the cytoplasm. The plasma also shows signs of shrinkage; some of the cells are quite spindle-shaped, and their texture is dense. We could see no satellitosis, neuronophagia, or ghost cells in these experiments of short duration.

It is also interesting that in experiments where the brain was examined within two or three hours after ultrasonic irradiation the vital staining and damage was seen only in the nerve cells, without any participation of the glia. The myelin sheaths, on the other hand, showed definite swelling and irregularity even at this early stage.

The capillaries looked normal within the small lesions. Their lumina were empty, due to the perfusion; their walls showed no anatomical changes and stained with trypan blue—a normal reaction. The perivascular space around larger vessels revealed no anatomical evidence of damage, such as enlargement or cellular infiltration.

On the basis of his own experiments and an extensive survey of the literature, Spatz [9] differentiates three types of vital staining in the central nerve tissue.

1. Diffuse imbibition of the tissue. This is a rapidly developing situation which consists of a very light blue discoloration for the entire tissue, without selective staining of the cells. It indicates, from a pathophysiological point of view, the penetration of the tissue by trypan blue, which escaped from the blood vessels as a result of damage and increased permeability of the blood-brain barrier. In our material this process alone can account for the diffuse staining of the lesion.

2. Granular or vacuolar incorporation. This stage is secondary to the diffuse imbibition. It consists of the uptake of the dye granules by normal cells. This is a process which involves only living cells and is characteristic of the glia. It takes at least 24 hours to develop after the injection of the dye, and consequently this stage was not encountered in the experiments reported here.

3. Diffuse coloration of the cells. In this process the entire cell stains deeply and diffusely, so that it forms a marked contrast with the faintly colored tissue background. This situation occurs very early after the injection of trypan blue and is a sign of severe cell damage. Such diffuse staining of cells could be seen in the neurons of our lesions, demonstrating the direct cell damage caused by ultrasound; on the other hand, the diffuse background staining of the entire tissue is evidence of the ultrasound-inflicted damage to the blood-brain barrier.

Occasionally the lesion was so slight that no trace of damage could be observed in either cell- or fiber-stained sections, in spite of clearly visible, minute trypan blue staining prior to sectioning.

Comment

The data obtained from these experiments indicate that within the area of damage caused by focused ultrasound the blood-brain barrier is altered and made easily permeable to trypan blue and radioactive phosphate. This results in local accumulation of the dye and in high concentration of P^{32} within the lesion. The time-concentration curves of the isotope in plasma, normal brain, and ultrasonic lesion give evidence of an abnormally rapid exchange of phosphate between plasma and lesion. Furthermore, after ultrasonic irradiation there is characteristically a fast initial uptake of phosphate, followed by a gradual decrease. While this is characteristic of most parenchymatous organs, normal brain takes up phosphate at a slowly increasing rate. Owing to ultrasonic tissue damage, it would seem that the injured area of the brain turns into a "non-barrier-protected" region. This is a common sequence of other severe cerebral injuries, and similar concentrations

of vital dyes and isotopes can be observed in lesions due to trauma, heat, and chemical, toxic, or allergic reactions.

Specific, and experimentally useful, however, is the relative ease with which ultrasonic lesions can be produced at predetermined sites and of variable magnitudes, without apparent damage to the blood-brain barrier and blood supply of tissues interposed between the ultrasonic applicator and the lesion. There is, for example, no needle tract and consequent barrier disruption between the deep lesion and the surface of the brain.

These experiments also furnished comparable data on the mode of action and extent of penetration into the brain of a vital dye (trypan blue), on the one hand, and of an isotope (P^{32}), on the other hand.

As one of us was able to point out previously,[1] there is a striking resemblance between the deposition of radioactive phosphate and that of vital dyes in those portions of the brain which do not seem to possess a protective barrier (choroid plexus, tuber cinereum, area postrema, etc.) and in the central nervous system proper provided that the barrier system is disrupted (by trauma, vascular disease, tumor, etc.). One can add to this statement the fact that no type of lesion has been found so far in the central nervous system in which high concentration of P^{32} or vital staining with trypan blue could be found alone, dissociated from one another.

Yet there is a profound, basic difference between the behavior of vital dyes and isotopes. In the case of trypan blue, we witness the action of the blood-brain barrier against an artificial agent of large molecular size which does not participate in cerebral metabolism. Its penetration is governed by an "all or none" law. It does not enter the nerve tissue under normal circumstances, but it penetrates if the permeability of the barrier increases. Radioactive phosphate, on the other hand, is an ion, interchangeable with nonradioactive phosphate, constantly present in large amounts in both plasma and brain and participating in fundamental metabolic actions of the central nervous system. There always is a direct or indirect interchange of plasma and brain phosphates; the change in barrier permeability reflects only an increase or decrease of this exchange.

Of great significance is the selective action of the blood-cerebrospinal fluid barrier on different substances. Although anatomically different, this barrier, together with the blood-brain barrier, comprises a physiological entity which provides a stable chemical environment for the vulnerable central nervous system. The difference between the passage of this barrier by trypan blue and P^{32} is even greater than that of the blood-brain barrier: It is quite impermeable to trypan blue, but phosphate passes it (through the vessels of the choroid plexus and meninges) fairly rapidly.

The similarity in the action of both trypan blue and radioactive phosphate as representatives of vital dyes and isotopes manifests itself in those regions of the brain where barrier permeability is increased. These involve, in addition to the specific areas of choroid plexus, tuber cinereum, area postrema, etc., cerebral injuries, cerebrovascular disorders, toxic damage, infections, and tumors. All these lesions are characterized by distinct trypan blue staining and by a large concentration of P^{32}. The onset of this deposition of vital dyes and that of P^{32} are equally rapid; it occurs within a few minutes following administration of the agent. However, the duration of deposition is different. The time limit of distinct trypan blue staining does not exceed 7 to 10 days, while significantly increased isotope concentration is detectable in a lesion for at least 2 months after injection of the tracer. The extent of barrier damage seems to be consistently larger when studied with P^{32} than when studied with vital staining. Comparative observations on ultrasonic lesions of the brain, using the two substances simultaneously, corroborates this statement. The lesions as outlined by darkening of the films on radioautographs were consistently larger than the corresponding

blue discoloration in the specimen. Naturally, one has to be very careful in this comparison. The radioautographic density is not an absolute and completely true image of the isotope concentration of a given area. It varies considerably with the size of grain and thickness of the emulsion on the film, with the length of exposure, and with the thickness of the specimen and its distance from the film. The resolution of the image is best when the thicknesses of sections and emulsions and the space between the two are reduced to a minimum. It is particularly difficult to obtain clear resolution in brain tissue (which tears easily) when using P^{32}, which has a high-energy beta radiation. For this latter reason nuclear tract determination, which would otherwise give very valuable data, is not feasible.

Nevertheless, we were able to make two observations relevant to these technical aspects. 1. P^{32} showed a larger-sized lesion than trypan blue even in 50μ sections, which yield good radioautographic resolution, with a minimal amount of scattered radiation. 2. There was a clear-cut increased density, characteristic of the lesion in sections which were taken just beyond the vitally stained portion, where actually no trypan blue could be detected.

The microscopic changes following ultrasonic irradiation of the cerebral gray and white matter were recently described in great detail by Barnard, Fry, and Brennan.[3] They state that the blood vessels in the white matter do not appear to be altered morphologically by ultrasound. No erythrocytes appear in the matrix of any white-matter lesions even 12 hours after exposure. Our experiments corroborate this observation. They indicate, however, that, notwithstanding the lack of visible change in the structure of irradiated capillaries, there is ample evidence of a profound disturbance in capillary or blood-brain-barrier permeability, as evidenced by the rapid and massive deposition in the brain of trypan blue and P^{32}. We therefore are led to conclude that the physiological capillary damage is probably just as severe as the neuronal damage and it is due only to the technical shortcomings of the conventional histological methods that the morphological evidence cannot be seen on routine microscopic examination. In addition, one can safely assume that the capillary damage is reversible over long periods of time, in contradistinction to the destruction of the nervous elements.

Actually, Barnard, Fry, and associates,|| found it conceivable that some of the edema which follows irradiation comes from a changed permeability of the capillaries. However, we cannot agree with their statement that the swelling of the perineuronal spaces leads to distortion of the shape of nerve cells. In our opinion, the latter is due to direct ultrasonic damage of the cells. It occurs simultaneously with the derangement of the blood-brain barrier, but is not necessarily caused by edema.

The island-and-moat pattern of heavy lesions cannot be explained easily, unless one invokes chemical changes preventing the action of proteolytic enzymes within the island. One possible factor appears to be overheating of the lesion's center. The resistance of gray matter to ultrasonic damage may be related to its smaller coefficient of ultrasonic absorption, together with the relative vascularity of the tissues, which would result in smaller amounts of ultrasonically produced heat and thus to a slowing down of reaction kinetics. It seems worth noting that the lateral geniculate body, which was found by us to be extremely radiation-resistant, is considered to be one of the most vascular regions of the cat's brain. This group of cells is supplied, according to the measurements of Campbell,[5] by two to three times as many capillaries as the basal ganglia, thalamus, and hippocampus, and its relative vascularity is even more pronounced when compared with the white matter of the centrum semiovale.

Summary

The effect of focused ultrasound on the blood-brain barrier was studied in cats. The

|| References 2 and 3.

animals were killed from 10 minutes to 5 days after irradiation, having received single intravenous injection of radioactive phosphate and trypan blue within 10 minutes to 3 hours before death.

Ultrasound-produced lesions stained selectively with trypan blue. They also revealed large P^{32} concentration as compared with the surrounding normal brain tissue. The variation of the P^{32} concentration of the lesions with time elapsed from the administration of the isotope directly follows the changes in plasma P^{32} concentration. Such a linear relationship does not exist between normal brain tissue and plasma. These observations point to a profound alteration of the blood-brain-barrier permeability within the confines of lesions produced by ultrasound.

Small lesions show a uniform deposition of trypan blue and P^{32}. Large lesions frequently reveal an "island-and-moat" pattern, with greater tissue destruction and tracer deposition in the moat than in the central island.

Gray matter, whether cortical or nuclear, was found to be more resistant to ultrasound than white matter.

The mode of actions and usefulness of trypan blue and P^{32} as tracers are compared and discussed.

The microscopic picture of cerebral damage produced by ultrasound is presented with special regard to the significance of vital staining and to the morphological changes of neurons.

W. J. H. Nauta, of the Department of Neurophysiology, Walter Reed Army Hospital, Washington, D. C., gave help in histological interpretation, and E. Francis and J. A. Rosenthal, of the Medical Acoustics Research Group, Massachusetts General Hospital, assisted in the experiments.

REFERENCES

1. Bakay, L.: The Blood-Brain Barrier, with Special Regard to the Use of Radioactive Isotopes, Springfield, Ill., Charles C Thomas, Publisher, 1956.

2. Barnard, J. W.; Fry, W. J.; Fry, F. J., and Krumins, R. F.: Effects of High Intensity Ultrasound on the Central Nervous System of the Cat, J. Comp. Neurol. 103:459-484, 1955.

3. Barnard, J. W.; Fry, W. J.; Fry, F. J., and Brennan, J. F.: Small Localized Ultrasonic Lesions in the White and Grey Matter of the Cat Brain, A. M. A. Arch. Neurol. & Psychiat. 75:15-25, 1956.

4. Broman, T.: Permeability of the Cerebrospinal Vessels in Normal and Pathological Conditions, Copenhagen, Ejnar Munksgaard Forlag, 1949.

5. Campbell, A. C. P.: Variation in Vascularity and Oxidase Content in Different Regions of the Brain of the Cat, Arch. Neurol. & Psychiat. 41:223-242, 1939.

6. Fry, W. J.; Mosberg, W. H.; Barnard, J. W., and Fry, F. J.: Production of Focal Destructive Lesion in the Central Nervous System with Ultrasound, J. Neurosurg. 11:471-478, 1954.

7. Hueter, T. F.; Ballantine, H. T., and Cotter, W. C.: Production of Lesions in the Central Nervous System with Focused Ultrasound: A Study of Dosage Factors, J. Acoust. Soc. America 78:192-201, 1956.

8. Jasper, H. H., and Ajmone-Marsen, C.: A Stereotaxic Atlas of the Diencephalon of the Cat, National Research Council of Canada, Ottawa, Ont., Canada.

9. Spatz, H.: Die Bedeutung der vitalen Färbung für die Lehre vom Stoffaustausch zwischen dem Zentralnervensystem und dem übrigen Körper, Arch. Psychiat. 101:267-358, 1933.

Studies on Lysergic Acid Diethylamide (LSD-25)

I. Effects in Former Morphine Addicts and Development of Tolerance During Chronic Intoxication

HARRIS ISBELL, M.D.
R. E. BELLEVILLE, M.A.
H. F. FRASER, M.D.
ABRAHAM WIKLER, M.D.
and
C. R. LOGAN, Lexington, Ky.

The striking mental changes induced by the diethylamide of lysergic acid (hereafter referred to as LSD) have been studied extensively in Europe,* Great Britain,† and the United States.‡ In minute doses (20γ to 120γ) LSD induces a peculiar mental state characterized by anxiety, signs of autonomic dysfunction, perceptual distortion (chiefly visual), alterations in mood and affect, synesthesias, feelings of depersonalization, and hallucinations. The drug is apparently the most effective and safest agent for inducing an experimental, but reversible, psychosis in nonpsychotic subjects.

Various interpretations have been placed on the mental state produced by LSD. Some European authors refer to it as a "toxic psychosis of the exogenous reaction type" or a "diencephalosis,"§ presumably because the autonomic signs suggest effects on the hypothalamus. The resemblance of some of the psychic manifestations which follow LSD to symptoms of the major psychoses has been stressed by others.‖ The LSD reaction has been referred to as "experimental schizophrenia" or "experimental psychiatry." Because some of the symptoms induced by LSD also occur in schizophrenia, it has been suggested that schizophrenia may be due to a toxin,[21] to a deficiency of some metabolite necessary for brain function,¶ or to some metabolic tissue disturbance.# A defect in the degradation of epinephrine involving either adrenochrome[25] or adrenoxine[26] has been postulated. Another hypothesis, based on competitive actions of serotonin and LSD in excised smooth muscle preparations, postulates either a deficiency or an excess of serotonin in the brain.[23] Recently it has been shown that both reserpine and serotonin prolong the sleeping time of mice treated with hexobarbital.[27] LSD abolishes the prolongation of sleeping time induced by either substance.* Since reserpine causes depletion of serotonin stores in the brain,† some relationship between serotonin and mental function is inferred. Further, LSD is presumed to cause mental symptoms by "competing with" serotonin for neuronal receptor sites.

All of these theories are based on resemblances between the LSD reaction and the major psychoses. The effects of LSD last only a few hours, and practically all experiments with the drug have been "acute"; i. e., single doses of LSD were given at intervals of days or weeks. The

Received for publication May 24, 1956.

From the National Institute of Mental Health, Addiction Research Center, U. S. Public Health Hospital.

* References 1-5.
† References 6-9.
‡ References 10-20.
§ References 1, 21.
‖ References 4, 12, 14.
¶ References 22, 23.
# References 5, 24.
* References 27, 28.
† References 28, 29.

chronic experiments that have been done involved administration of the drug to psychotic patients in whom the LSD response was difficult to assess. It, therefore, seemed desirable to determine whether resemblance of the LSD reaction to the major psychoses, which are chronic diseases, would become more or less prominent when the drug was administered chronically to nonpsychotic persons. It is the purpose of this paper to describe the reaction induced by LSD in former morphine addicts, to show that the intensity of the reaction is measurable, and to report the rapid development of tolerance (loss of effect) to LSD when the drug was administered daily for 3 to 85 days.

Characteristics of the LSD Reactions in Former Opiate Addicts

The patients who volunteered for the experiments were male drug addicts who had been abstinent from opiates for three months or more when the studies were carried out. None of these patients was psychotic; all had either character disorders or inadequate personalities, and the majority were Negroes. Because of the great differences in economic and ethnic backgrounds and personality types, and, possibly, physiological differences resulting from antecedent opiate addiction, it was necessary to determine whether the LSD reaction in these subjects was similar to the reactions observed by other investigators in other kinds of people in different environments. Preliminary experiments were, therefore, carried out using 12 white and 12 Negro male subjects.

Methods.—The experiments were conducted in a closed ward devoted to clinical research. The subjects were observed in individual rooms but were free to leave between observations and to mingle with other patients in a common dayroom. The drug was always given orally, and the subjects were fasting. Doses of LSD varied from 20γ to 300γ (total dose), or approximately 0.25γ to 5γ per kilogram of body weight. Results were controlled by using placebos and a randomized order of administration of LSD and placebos in all experiments. Pulse rate, systolic and diastolic blood pressures, respiratory rate, and rectal temperature were determined at hourly intervals, after 10 minutes' rest in bed, and 2 hours before and 8 hours after administration of either placebo or LSD. Brief psychiatric examinations were carried out approximately two, four, and six hours after administration of the drug. Pupillary diameter was determined once hourly, as follows: The patient was taken into a dark room, seated in a chair under constant light, and asked to look at a white spot on a wall 10 ft. (3 meters) away. The size of the pupils was compared with those of black circles of known diameter on a card which was held alongside the patient's eyes. Neurological examinations, including pupillary reactions to light and accommodation, station and gait, coordination, deep tendon and superficial skin reflexes, and tests for abnormal reflexes were carried out hourly.

Results.—Response to Various Doses: Reactions to zero dosage (placebo) were generally negligible. Doses of LSD of less than 1γ/kg. of body weight induced only mild effects. Autonomic changes were slight. Mental effects consisted chiefly of anxiety and mood changes, primarily in the "euphoric" direction. Perceptual distortion was rare, and no hallucinations were reported. Doses of 1γ to 2γ per kilogram induced more striking effects. The autonomic and neurological changes became definite and measurable. Mental changes, including anxiety, mood changes, and perceptual distortion, occurred in all patients, and many reported "elementary" hallucinations (kaleidoscopic patterns of light and color with the eyes closed) and occasionally "true hallucinations" (perception of something that could be described as a definite thing, animal, or person). Feelings of unreality and symptoms of depersonalization were common.

Doses of 3γ/kg. or more induced a reaction which was too severe to be tolerated on more than one occasion by most patients. A dosage range of 1γ to 2γ per kilogram was adopted for most work, and the descriptions below are based on doses of this order.

Time Course: The effects of 1γ to 2γ of LSD per kilogram were apparent within 30 minutes after oral administration, became maximal in one and one-half to two hours, remained maximal to the fourth or fifth hour after administration, and thereafter gradually declined. Usually, eight hours after the drug patients had recovered except for some residual nervousness and anxiety. All symptoms disappeared completely within 16 hours.

"Nonmental" Effects: Statistical analysis of the data showed no significant change in temperature, pulse rate, or respiratory rate. Systolic and diastolic blood pressures were significantly elevated.

The only consistent neurological changes were dilatation of the pupils and accentuation of the deep tendon reflexes. Occasionally, twitching of the muscles and tremors involving muscle clonus occurred in patients who had severe mental reactions. Waves of goose flesh were noted in some patients.

"Mental" Effects: The mental effects seemed to be identical with those described in the literature in nonaddicts. Changes in mood in the direction of either euphoria or depression, difficulty in concentration, feelings of strangeness, anxiety, nervousness, and dream-like states were reported. Motor activity varied. Some patients were constantly active; others became very quiet and withdrawn.

Various alterations in all sensory modalities were described: acute or dull hearing, "sandpaper" feel of clothes, metallic tastes, bad odors, sensations of the body being light or heavy, and a great variety of visual changes. Actually, alteration in vision was the only sensory change reported by all patients. The subjective visual phenomena included blurring; changes in perception of depth and distance; distortion in size, shape, and color of objects, persons, and the patient's own body; lights and colors on closing the eyes or looking at the wall, which formed kaleidoscopic patterns not suggestive of any real thing ("elementary hallucinations"), and, rarely, "true hallucinations" (perception of persons or things not really present). Frequently, patients saw their hands or feet transformed into animal paws or into the extremities of a dead person. Similar sensations were experienced on looking at other persons. Auditory hallucinations were infrequent. The sensorium was clear, and insight (realization that the effects were due to the drug) was usually maintained. Affect, though difficult to judge, generally seemed appropriate. During marked reactions most patients expressed fears of dying or of becoming permanently insane.

Symptoms which might be classed as "depersonalization" included the changes in the appearance of the extremities described above, "feelings" of being outside one's own body, and difficulty in recognizing oneself in a mirror. Patients also mentioned difficulties in deciding whether a thought referred to a real event or object or was merely a thought. Such experiences, while puzzling, did not form a part of an organized delusional system. Patients usually stated that such phenomena had not really occurred and were due to the drug.

Marked quantitative variations in the degree of reaction of different subjects to the drug were noted. A dose of 2γ/kg. might induce only nervousness in one subject, while another subject might experience perceptual distortion and true hallucinations with loss of insight on the same dose. The same subject, however, responded each time to the same degree and in the same way as long as the testing situation was held constant.

Psychological Tests: In a preliminary exploratory experiment, six Negro males were given a battery of psychological tests (Wechsler-Bellevue Intelligence Scale, Goldstein-Scheerer Cube and Color-Form Sorting Test, the Rorschach test, and the Minnesota Multiphasic Personality Inventory [MMPI]) while receiving no drug and again at the height of the LSD reaction, after receiving a dose of 1γ to 2γ/kg. of LSD.

Comparison of the Wechsler-Bellevue subtest scores and the intelligence quotients obtained under control conditions (no drugs) with those following LSD showed a decrease in all verbal subtest scores. Scores on all performance tests, except the digit symbol, increased slightly, but the increases were less than those expected from the practice effects. When corrected for the expected practice effects, all subtest scores showed some decrease after LSD. When

the intelligence quotients after LSD were corrected for the expected practice effect, the verbal I. Q. decreased 8.63 points, the performance I. Q. 6.07 points, and the full-scale I. Q. 7.43 points. Although the number of subjects is small, these decreases probably represent a substantial impairment of intellectual function.

No loss of conceptual or abstract ability was found on repetition of the Goldstein-Scheerer Cube and Color-Form tests during LSD intoxication. However, it was apparent that patients exerted a great deal of effort in order to complete the tasks. Much of the effort took the form of acquiring a "set," i. e., making bodily adjustments indicating an attitude of attention. Possibly, this effort was related to difficulty in concentrating.

When responses on the Rorschach test before and after LSD administration were compared, some variation in several of the scoring categories was observed in each patient. However, the basic pattern of the test responses remained the same. When the Rorschach tests of all six patients were analyzed as a group, changes were noted in several factors under LSD: There was a decrease in total number of responses (R), in F+ per cent, and in Z (organizational activity), and a trend toward a D approach at the expense of W. Perhaps the most significant effect was a decrease in the use of form and an increase in the use of factors other than form. In every subject, either Sum C or Sum Y was increased. Although the changes can be considered only as trends because of the small number of subjects, they seem to indicate increased emotionality and a breakdown or loosening of intellectual control in patients who characteristically maintained rigid control.

Such striking changes were observed in the MMPI profiles after LSD in the original six subjects that it appeared the MMPI might be more sensitive than other psychological tests in measuring the LSD response. A separate study, which is being reported in detail elsewhere,‡ was therefore undertaken. Briefly, 24 subjects were tested in random balanced order under no drug, placebo, and LSD (50γ-130γ) conditions. The MMPI was given one and one-half hours after administration of placebo or LSD. Statistically significant elevations were found in the Psychasthenia ($P<0.01$), Schizophrenia ($P<0.01$), Paranoia ($P<0.05$), and Taylor Anxiety Scales ($P<0.05$).

Methods of Measurement and Analysis

On the basis of the preliminary work described above, methods for measuring both the "mental" and the "nonmental" aspects of the reaction were developed. Pupillary diameter, systolic blood pressure, and change in patellar reflexes were chosen as objective and measurable signs of the LSD reaction. Systolic blood pressure was measured after 10 minutes' rest in bed, using the standard auscultatory method. Pupillary diameter was estimated as described above. Patellar reflexes were graded according to the following system:

Grade 0: No response elicitable, even with reinforcement

Grade 1: Response elicitable only with reinforcement

Grade 2: Response elicitable without reinforcement; excursion after light tap less than a 6-in. arc and not repetitive

Grade 3: Response elicitable with light tap; excursion greater than 6-in. arc

Grade 4: Response very quick, forceful, and repetitive; almost complete extension of leg

These measurements were made at hourly intervals for two hours before and eight hours after administration of LSD. Data obtained were plotted on graph paper and the area under each curve measured with a planimeter, thus summarizing the data for each particular measurement in one figure. The average of the pre-drug measurements was used as the base line in each case.

Mental effects induced by LSD were assessed in two ways: 1. The questionnaire devised by Abramson and associates[19] was administered hourly for two hours before and for eight hours after LSD. The number of positive responses on the questionnaire was counted over the entire eight-hour period after administration of LSD, but answers to questions which were also scored positive before administration of the drug were eliminated. The questionnaire includes such items

‡ Belleville, R. E.: MMPI Score Changes Induced by Lysergic Reid Dithylamide (LSD-25), to be published.

as "I am trembling inside," "I am confused," "Things seem near or far away," etc. This questionnaire has several disadvantages—it may suggest symptoms; few positive responses are given to many of the questions, and it does not cover all the mental phenomena observed after LSD. The questionnaire, however, has the advantage that a systematic record of certain symptoms is obtained at definite intervals before and after administration of the drug.

2. The degree of mental effect was also assessed by conducting a short psychiatric examination between the second and fourth hour after administration of the drug. In carrying out this examination, special attention was given to anxiety, nervousness, perceptual distortion, presence or absence of hallucinations, and insight, and a "grade" was assigned to the reaction according to the following scheme:

Grade 1: Anxiety and nervousness, without perceptual distortion or hallucinations

Grade 2: Anxiety, nervousness, and visual perceptual distortion without "true" hallucinations

Grade 3: Anxiety, nervousness, perceptual distortion, and "true" hallucinations, but with insight maintained

Grade 4: Same as Grade 3, except that insight (realization that the effects are due to the drug) is lost

The grading system was based on the time course and on the response to increasing dosage observed in the preliminary work. The system has the disadvantage that the various grades may not form a continuous scale (Grade 2 may not be twice that of Grade 1). It gives no information concerning the quantitative aspect of the symptoms which go into determining the grades. Also, Grade 4 was seldom reached with doses of less than 3γ/kg.

These methods were tested by determining the response to graded doses and by determining the reproducibility of the reaction in the same subjects.

Response to Varying Doses.—Eight nontolerant Negro males were used in this experiment. They were given, under "blind" conditions and in randomized order at weekly intervals, a placebo and 0.25γ, 0.5γ, 0.75γ, 1γ, 1.5γ, and 2γ per kilogram of body weight of LSD. Two of the patients, who were very sensitive to LSD, did not receive the 2γ dose, and one did not receive the 1.0γ dose. Observations were carried out as described above. Results obtained with the various doses are shown in Table 1. Allowing for the omission of the sensitive patients in the 1.5γ and 2γ columns, the degree of change in all measurements increased with the dose. Peak effects were attained at the 1.5γ/kg. dose except for blood pressure. Statistical analysis, using a *t*-test for paired observations[30] showed that changes from placebo to LSD were significant ($P<0.05$) for all measurements at all doses except 0.25γ/kg. Differences between doses that varied as much as 1γ/kg., e. g., between 1.0γ/kg. and 2.0γ/kg., were statistically significant, whereas differences between doses varying 0.5γ/kg. or less, e. g., between 0.5γ/kg. and 1.0γ/kg., were not significant.

Although the number of patients used was small, the results showed that the degree of effect was related to the dose and that methods were useful in assessing the intensity of the LSD response.

TABLE 1.—*Effects of Increasing Doses of LSD-25*

Measure	Dose, γ/Kg.						
	0	0.25	0.5	0.75	1.0*	1.5	2.0†
Patellar reflex‡	0.5	1.18	1.60	1.89	2.10	2.04	1.93
Pupillary diameter‡	0.4	1.10	2.29	3.57	3.64	4.27	3.66
Blood pressure‡	1.82	2.91	2.93	4.00	4.24	4.87	5.35
Questions§	4	26	42	56	30	65	42
Grade§	0	0.2	0.63	1.5	0.7	1.6	1.5

* Data on seven patients only.
† Data on six patients only.
‡ Expressed as mean area under curve (square inches). See text.
§ See text for method.

Reproducibility.—Twelve Negro males received 60γ of LSD on three separate occasions at intervals of at least one week. Tests with LSD were interspersed in randomized order with placebos. The results were analyzed as described above and are shown in Table 2. Statistically, the results were identical on all three tests, thus proving that the measurements used in assessing the LSD reaction are reproducible in the same subjects from time to time, provided test conditions are held the same.

TABLE 2.—*Reproducibility of Response to 60γ LSD on Three Separate Occasions*

Measure	Trial		
	1	2	3
Patellar Reflex*	3.32±0.47	3.01±0.38	3.01±0.52
Pupillary Diameter*	3.02±0.20	3.73±0.37	3.02±0.18
Blood Pressure*	2.40±0.36	2.30±0.18	2.39±0.38
Questions†	101±24	97±29	93±19
Grade†	1.5 ±0.32	1.1 ±0.3	1.5 ±0.11

* Expressed as the mean ± the standard error of the area under curves (square inches).
† Means ± standard errors. For methods, see text.

Tolerance

Four experiments were carried out. In Experiments 1 and 2, the period of administration of LSD was relatively short, and questionnaires and assessment of the clinical degree of reaction were the only measurements obtained. In Experiments 3 and 4, administration of LSD was carried on for longer periods of time, and measurements included effects on blood pressure, pupillary diameter, and knee jerk. In the fourth experiment a special effort was made to assess the degree of tolerance and to determine the speed with which tolerance was lost on discontinuation of the drug.

EXPERIMENT 1.—Five Negro males and six white males received in randomized order for three days either a placebo or LSD twice daily. LSD was administered in doses of 10γ, 20γ, and 30γ at 9 a.m. and 9 p.m. on the first, second, and third days, respectively. On the fourth day all patients were given 75γ of LSD (approximately 1γ/kg.) at 9 a.m., and questionnaires and clinical rating were obtained as described above. During the following week the experiment was repeated except that those patients who had received LSD were given placebos and vice versa. Results are shown in line 1 of Table 3. The decreases in the number of positive questions and in the clinical grade observed after three days' pretreatment with LSD as compared with three days' pretreatment with placebos were significant ($P<0.05$) by the *t*-test for paired observations.[20]

EXPERIMENT 2.—Four white and 4 Negro males received in randomized order either placebos or LSD at 9 a.m. daily for seven days. The initial dose of LSD was 20γ, increasing stepwise to 75γ on the seventh day. On the eighth day all patients

TABLE 3.—*Tolerance to LSD After Administration for Three Days (Experiment 1) and Seven Days (Experiment 2)**

Experiment	Questions		Clinical Grade	
	Nontolerant†	Tolerant‡	Nontolerant†	Tolerant‡
1	98±25	22±9	1.95±0.35	0.6±0.2
2	88±31	18±5	1.7 ±0.5	0.6±0.2

* Figures are the means ± standard errors.
† After administration of placebo for three or eight days.
‡ After administration of LSD for three or eight days.

in both groups were tested with 75γ of LSD, and questionnaires were obtained and clinical grades assessed. In the second half of the experiment, the LSD and placebo groups were reversed. Results are shown in line 2 of Table 3. Significant decreases in both questions ($P<0.05$) and grade ($P<0.01$) were observed, which, however, were no greater than that seen after the three-day schedule described in Experiment 1.

EXPERIMENT 3.—Six Negro males served as subjects for this experiment. Five of these had been diagnosed as having character disorders and one as having an inadequate personality. No evidence of psychosis was found on psychiatric examination of any of these patients. Intelligence quotients ranged from 84 to 125. Prior to chronic intoxication, patients were tested at weekly intervals and in randomized order with doses of 0, 90γ to 130γ, 140γ to 150γ, and 180γ of LSD (approximately 1γ to 1.5γ, 1.5γ to 2γ and 2γ to 3γ per kilogram). Measurements were made as described above. Following completion of the initial testing, five patients were placed on a single daily dose of 90γ to 130γ of LSD once daily for seven to eight days. The dose was then increased to 150γ for three days and then to 180γ for three days. One of these five patients withdrew after the ninth day. The sixth patient, who had a very severe reaction to the 180γ test dose, began chronic intoxication with a dose of 50γ of LSD, which was gradually increased to 180γ by the 22d day of chronic intoxication. Questionnaires were obtained daily, and the clinical grade was assessed daily. Pupillary size, knee jerks, and blood pressure were measured at intervals of three to four days. At the end of the 14 days of chronic administration in four patients and of 22 days of chronic intoxication in one patient, LSD was discontinued without the patients' knowledge, water being given in its place. Five patients were tested with a single dose of 120γ to 130γ two to six days after discontinuation of LSD.

Results.—The results are protrayed graphically in Figure 1. On the left, in individual blocks, are shown the mean responses of the six patients to the three doses of LSD and to placebo prior to chronic intoxication. The results on patellar reflex, pupillary size, and systolic blood pressure are expressed in terms of the area under the time action curves (see "Methods

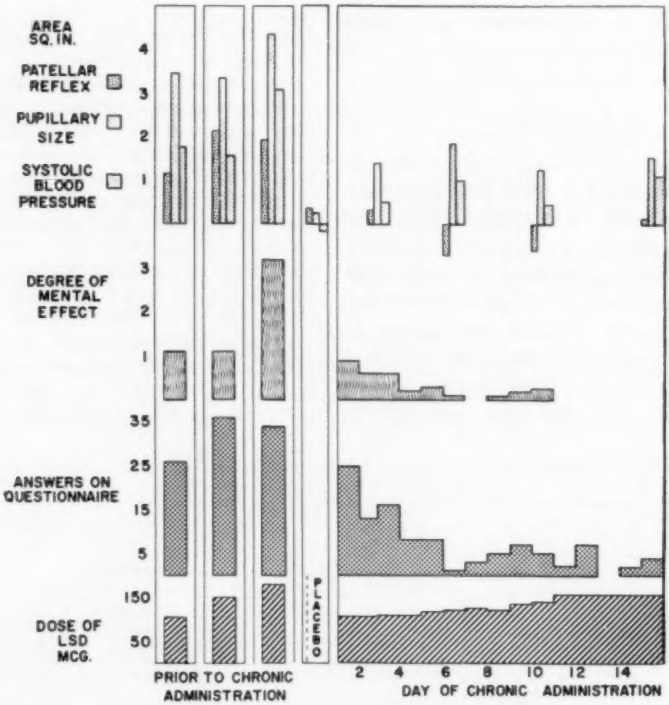


Fig. 1.—Tolerance to LSD in Experiment 3.

of Measurement"). Degree of mental effect and number of positive answers were assessed as described above. The mean responses to LSD during chronic administration are shown on the right, in the large block. In reading the Figure, it is necessary to remember that one patient withdrew after the ninth day and that the measurements obtained during only the first 14 days of chronic intoxication of the patient who received the drug for 22 days are included in the values shown. A rapid decline in the degree of response during chronic administration, despite the increase in the dose of LSD, is obvious. Statistical analysis, using a method for paired observations,[30] showed that the differences between the results before and after three days or more of chronic administration were highly significant statistically ($P<0.01$) for all measurements.

Patients did not notice the transition from LSD to water at the end of the period of chronic intoxication. The reaction was as intense three days after discontinuing LSD as prior to chronic intoxication.

The development of tolerance can best be illustrated by comparing the reaction of one patient to a dose of 180γ before and during chronic intoxication. When this dose was given prior to chronic intoxication, the patient became extremely anxious and felt that he was being shocked with electricity. His body seemed to shrink and enlarge. His hands appeared to have extra fingers. People and objects changed size, shape, and color. The walls were a flickering mass of shadows and colors. He felt that he would die or would become permanently insane. Blood pressure was elevated 60 mm. of mercury; pupils were maximally dilated; knee jerks were very hyperactive; spontaneous tremors of large muscle groups were observed, and ankle clonus could be elicited. After recovery from this severe reaction, the patient wished to drop out of the experiment but, after considerable persuasion, agreed to continue. He was started on 50γ of LSD once daily, and this dose was increased until he again received 180γ of LSD on the 22d day. At this time he had no subjective effects, sat quietly, read, and watched television. His reflex, pupillary, and blood pressure changes were minor.

EXPERIMENT 4.—This experiment was similar to Experiment 3 but was more prolonged. Seven Negro male subjects, all of whom had been diagnosed as having character disorders, served as subjects. Intelligence quotients ranged from 71 to 128. None of the patients presented any evidence of psychosis on psychiatric examinations. In one patient the results of the Wechsler-Bellevue Intelligence Scale was suggestive of an organic intellectual defect. This patient had a history of a head injury with a period of unconsciousness for several hours. Neurological and spinal fluid examinations were completely negative in this patient.

Prior to chronic intoxication with LSD, all seven subjects were repeatedly tested with doses of 1γ to 2γ of LSD per kilogram. Intensity of the reaction was assessed as described above. Patients were then placed on one dose of the drug daily, the mean dose being 1.28γ/kg. daily. After seven days the mean dosage was increased to 1.55γ/kg. This level was maintained for 77 days, except as specified below. The degree of effect induced by the original mean dose of 1.28γ/kg. was assessed on the 7th day of chronic intoxication, and the degree of the effect induced by the mean dose of 1.55γ/kg. was measured on the 14th and 21st days. Thereafter the 1.55γ/kg. level was maintained, and at intervals of two weeks the patients were tested with a double (3γ/kg.), triple (4.5γ/kg.), and quadruple (6γ/kg.) dose in an effort to assess the degree of tolerance which had been developed. After these tests had been completed, the drug was withdrawn without the patients' knowledge for periods of one, two, and three days. The patients were then tested with the original mean dose of 1.28γ/kg. of LSD. Between withdrawals of LSD, the patients were made tolerant again by administration of the 1.55γ/kg. dose daily. The drug was finally withdrawn completely and the experiment terminated.

Results.—The results are shown in Figure 2. In this Figure the mean results prior to chronic intoxication are shown in the first block; the means of the tests carried out during the first 21 days of chronic intoxication are shown in the second, third, and fourth blocks. The fifth, sixth, and seventh sections show the results after the double, triple, and quadruple doses of LSD. The final three sections show the results after

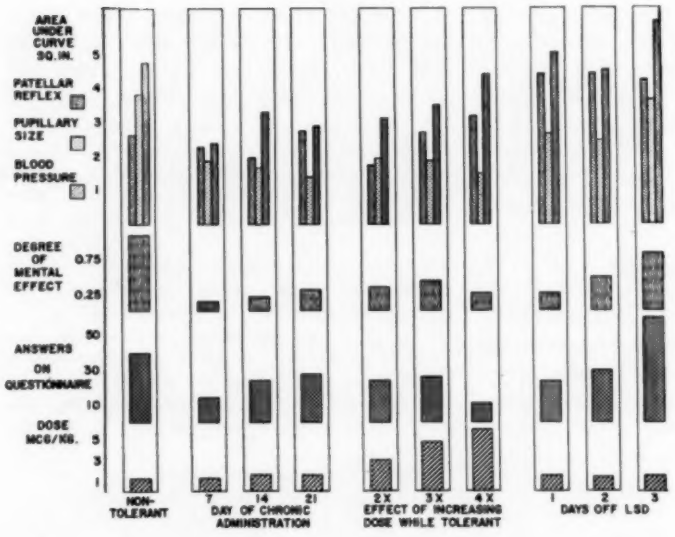


Fig. 2.—Tolerance to LSD in Experiment 4.

withdrawal of LSD for one, two, and three days, respectively. Decline in the LSD effects during the first 21 days of chronic intoxication is apparent. All decreases from preintoxication means are statistically significant. In this experiment, the degree of tolerance to the effects of LSD on knee jerks, pupillary size, and blood pressure, while definite, seemed less than in Experiment 3. Almost complete tolerance to the "mental" effects was developed, since the double, triple, and quadruple doses of LSD did not restore the original degree of mental reaction. Tolerance, however, was lost as rapidly as it was gained, since the original degree of mental reaction had been restored by the third day after discontinuation of LSD.

No abstinence symptoms followed withdrawal of LSD in either Experiment 3 or Experiment 4. In fact, none of the patients realized that LSD had been replaced by a placebo.

Comment

The effects induced by LSD appear to be the same in former opiate addicts as in nonaddicts, despite great differences in ethnic backgrounds, socioeconomic status, life history, personality patterns, and the environment in which testing with LSD was carried out. This fact indicates that the LSD reaction is, to some extent, independent of these variables. The LSD reaction appears to be a specific toxic psychosis which is mimicked only by intoxication with mescaline. It differs in its clinical features from the toxic psychoses induced by scopolamine, cannabis, cocaine, or withdrawal of alcohol and barbiturates.

Under the conditions of these experiments, the LSD reaction, when viewed *in toto*, had only a superficial resemblance to the chronic forms of any of the major psychoses. Symptoms suggesting schizophrenia which occurred in various patients included depersonalization, derealization, confusion, withdrawal from other persons, and changes in response to psychological tests. Affect, however, usually seemed appropriate, and auditory hallucinations were rare, as were ideas of reference and control. Systematized delusions were never observed. The outstanding change after LSD appears to be visual perceptual distortion. The kaleidoscopic changes in size, form, and color of objects, persons, and the patient's own body are very characteristic of the

LSD psychosis and are not a common part of the symptomatology of schizophrenia. The neurological signs induced by LSD are also not found in schizophrenia.

If it had been possible to maintain the original degree of effect throughout the experiment, the resemblance of the LSD psychosis to schizophrenia might have become more pronounced. It is conceivable that schizophrenia is associated with some chronic perceptual disorder and that a person who is having peculiar sensory experiences may develop peculiar explanations for these experiences. Such explanations might be interpreted by a person who is not experiencing such distorted perception as delusional thinking, and hence as evidence of schizophrenia.

The data establish the development of tolerance to LSD unequivocally. Two other laboratories § have also demonstrated this phenomenon in human subjects, and another has shown tolerance to the pyretogenic effect of LSD in rabbits.[33] Tolerance to LSD develops more rapidly, is greater in degree, and is lost more rapidly than is tolerance to any other drug with which we are familiar. Tolerance to LSD is not associated with the development of physical dependence (symptoms on withdrawal of the drug) as it is in morphine, barbiturates, and alcohol addictions. The data shed no light on the mechanisms of the tolerance. Further neurophysiological, biochemical, and psychological studies will be necessary to elucidate the reason for the declining effect of LSD on chronic administration.

Summary

In former opiate addicts, the diethylamide of lysergic acid (LSD-25) induced anxiety, mood changes, feelings of unreality, visual perceptual distortion, optical hallucinations, depersonalization, and derealization. Concomitantly, resting blood pressure was elevated, pupils were dilated, and the tendon reflexes were accentuated. Characteristics of the LSD reaction appeared to be the same in former opiate addicts and in nonaddicts.

The degree of both the "mental" and the "nonmental" changes increased with the dose of LSD. The intensity of the reaction induced by LSD remained the same when the same dose was repeated after an interval of a week or more.

When LSD was given daily, tolerance was evident after administration for only three days. After tolerance was well developed, administration of as much as four times the standard dose of LSD did not restore the original intensity of the reaction. On discontinuation of LSD, tolerance was lost as rapidly as it was developed.

§ References 31, 32.

REFERENCES

1. Stoll, W. A.: Lysergsäure-diäthylamid, ein Phantastikum aus der Mutterkorngruppe, Schweiz. Arch. Neurol. u. Psychiat. 60:279, 1947.

2. Becker, A. M.: Zur Psychopathologie der Lysergsäurediäthylamidwirkung, Wien. Ztschr. Nervenh. 2:402, 1949.

3. Condrau, G.: Klinische Erfahrungen an Geisteskranken mit Lysergsäurediäthylamid, Acta psychiat. et neurol. 24:9, 1949.

4. Fischer, R.; Georgi, F., and Weber, R.: Psychophysische Korrelationen: VIII. Modellversuche zum Schizophrenieproblem: Lysergsäurediäthylamid und Mezcalin, Schweiz. med. Wchnschr. 81:817, 1951.

5. Arnold, O. H., and Hoff, H.: Untersuchungen Über die Wirkungsweise von Lysergsäurediäthylamid, Wien. Ztschr. Nervenh. 6:129, 1953.

6. Mayer-Gross, W.: Experimental Psychoses and Other Mental Abnormalities Produced by Drugs, Brit. M. J. 2:317, 1951.

7. Sandison, R. A.: Psychological Aspects of the LSD Treatment of the Neuroses, J. Ment. Sc. 100:508, 1954.

8. Sandison, R. A.; Spencer, A. M., and Whitelaw, J. D. A.: The Therapeutic Value of Lysergic Acid Diethylamide in Mental Illness, J. Ment. Sc. 100:491, 1954.

9. Liddell, D. W., and Weil-Malherbe, H.: The Effects of Methedrine and of Lysergic Acid Diethylamide on Mental Processes and on the Blood Adrenaline Level, J. Neurol. Neurosurg. & Psychiat. 16:7, 1953.

10. Busch, A. K., and Johnson, W. C.: LSD-25 as an Aid in Psychotherapy, Dis. Nerv. System 11:2, 1950.

11. Forrer, G. R., and Goldner, R. D.: Experimental Psychological Studies with Lysergic Acid Diethylamide (LSD-25), A. M. A. Arch. Neurol. & Psychiat. 65:581, 1951.

12. DeShon, H. J.; Rinkel, M., and Solomon, H. C.: Mental Changes Experimentally Produced by L.S.D. (d-Lysergic Acid Diethylamide Tartrate), Psychiat. Quart. 26:33, 1952.

13. Savage, C.: Lysergic Acid Diethylamide (LSD-25): A Clinical-Psychological Study, Am. J. Psychiat. 108:896, 1952.

14. Rinkel, H.; DeShon, H. J.; Hyde, R. W., and Solomon, H. C.: Experimental Schizophrenia-like Symptoms, Am. J. Psychiat. 108:572, 1952.

15. Hoch, P. H.; Cattell, J. P., and Pennes, H. H.: Effects of Mescaline and Lysergic Acid (d-LSD-25), Am. J. Psychiat. 108:579, 1952.

16. Rinkel, M.; Hyde, R. W.; Solomon, H. C., and Hoagland, H.: Experimental Psychiatry: II. Clinical and Physio-Chemical Observations in Experimental Psychosis, Am. J. Psychiat. 111:881, 1955.

17. Savage, C.: Variations in Ego Feeling Induced by D-Lysergic Acid Diethylamide, Psychoanalyt. Rev. 42:1, 1955.

18. Landis, C., and Clausen, J.: Certain Effects of Mescaline and Lysergic Acid on Psychological Functions, J. Psychol. 38:211, 1954.

19. Abramson, H. A.; Jarvik, M. E.; Kaufman, M. R.; Kornetsky, C.; Levine, A., and Wagner, M.: Lysergic Acid Diethylamide (LSD-25): I. Physiological and Perceptual Responses, J. Psychol. 39:3, 1955.

20. Abramson, H. A.; Kornetsky, C.; Jarvik, M. E.; Kaufman, M. R., and Ferguson, M. W.: Lysergic Acid Diethylamide (LSD-25): XI. Content Analysis of Clinical Reactions, J. Psychol. 40:53, 1955.

21. Blickenstorfer, E.: Zum ätiologischen Problem der Psychosen vom akuten exogenen Reaktionstypus: Lysergsäurediäthylamid, ein psychisch wirksamer toxischer Spurenstoff, Arch. Psychiat. 188:266, 1952.

22. Woolley, D. W., and Shaw, E.: A Biochemical and Pharmacological Suggestion About Certain Mental Disorders, Proc. Nat. Acad. Sc. 40:228, 1954.

23. Woolley, D. W., and Shaw, E.: Some Neurophysiological Aspects of Serotonin, Brit. M. J. 2:122, 1954.

24. Mayer-Gross, W.; McAdam, W., and Walker, J.: Lysergsäure-diäthylamid und Kohlenhydratstoffwechsel, Nervenarzt 23:30, 1952.

25. Hoffer, A.; Osmond, H., and Smythies, J.: Schizophrenia; A New Approach: II. Result of a Year's Research, J. Ment. Sc. 100:29, 1954.

26. Rinkel, M.; Hyde, R. W., and Solomon, H. C.: Experimental Psychiatry: III. A Chemical Concept of Psychosis, Dis. Nerv. System 15:259, 1954.

27. Shore, P. A.; Silver, S. L., and Brodie, B. B.: Interaction of Serotonin and Lysergic Acid Diethylamide (LSD) in the Central Nervous System, Experientia. 11:272, 1955.

28. Shore, P. A.; Silver, S. L., and Brodie, B. B.: Interaction of Reserpine, Serotonin, and Lysergic Acid Diethylamide (LSD) in the Central Nervous System, Science 122:284, 1955.

29. Pletscher, A.; Shore, P. A., and Brodie, B. B.: Serotonin Release as a Possible Mechanism of Reserpine Action, Science 122:374, 1955.

30. Edwards, A. L.: Statistical Analysis for Students in Psychology and Education, New York, Rhinehart & Co., Inc., 1946.

31. Cholden, L. S.; Kurland, A., and Savage, C.: Clinical Reactions and Tolerance to LSD in Chronic Schizophrenia, J. Nerv. & Ment. Dis. 122:211, 1955.

32. Abramson, H. A.; Jarvik, M. E.; Garin, M. H., and Hersch, M. W.: Lysergic Acid Diethylamide (LSD-25): XVII. Tolerance Development and Its Relationship to a Theory of Psychosis, J. Psychol. 41:81, 1956.

33. Gogerty, J. H., and Dille, J. M.: Tolerance to the Pyretogenic Effects of Lysergic Acid Diethylamide, J. Pharmacol. & Exper. Therap. 116: 450, 1956.

Temporal Lobectomy with Removal of Uncus, Hippocampus, and Amygdala

Results for Psychomotor Epilepsy Three to Nine Years After Operation

ARTHUR A. MORRIS, M.D., Washington, D. C.

Five years have elapsed since my initial report on the results of temporal lobectomy for psychomotor epilepsy (Davidson Lecture).[1] Bailey and Gibbs *; Green, Duisberg, and McGrath [3]; Bailey, Green, Amador, and Gibbs,[4] and others † have reported their results. Encouraging results have been obtained, and each investigator has cautioned against premature conclusions. I cannot emphasize too strongly that the operations employed in my series are considerably different from those used by other workers. The uncus, the hippocampal gyrus, and the amygdaloid nucleus were also removed during each of the "standard" operations.

This report concerns 36 private patients having uncontrollable psychomotor seizures who have been subjected to temporal lobectomy. The average follow-up period since operation is five years (first operation, Oct. 27, 1946; last, Oct. 21, 1952).

The basis of removing epileptogenic foci associated with pathological lesions has been carefully formulated by Penfield and his co-workers.‡ But as late as 1952 Penfield had concluded that "excision of normal cerebral cortex rarely, if ever, gives a good therapeutic result."[12] Previously, Gibbs and co-workers [13] had established the relationship between the anterior portion of the temporal lobe and psychomotor epilepsy (either in pure form or in association with convulsions). Bailey and Gibbs [2] later reported on temporal lobe operations in 25 patients and found only 14 patients with gross pathological lesions. Later, Bailey, Green, and associates [4] commented that the chances of obtaining a good therapeutic result were greater when a pathological lesion was present than when the only evidence of abnormality was electroencephalographic. Thus, excision of normal cerebral cortex was made on the basis of electroencephalographic evidence, and some good results were obtained. This fact initially occurred to me during study with Pope, Jasper, Elliott, and Penfield,[14] who showed that after implantation of alumina-cream-filled linen discs in monkeys focal, clinical, chemical, electroencephalographic, and pathological correlates of human focal epilepsy were found. In one animal a "mirror" electroencephalographic focus was induced, and the seizures subsequently changed from focal to generalized. Excision of the primary focus caused disappearance of the "mirror focus" after one month. The animal remained free from seizures for two years, when it was killed. Yet at autopsy the "mirror" focus appeared pathologically

Received for publication Sept. 15, 1955.

This study was supported in part by a grant from the Doctors Hospital Research Foundation.

Chief of Neurosurgery, Doctors Hospital; Instructor Neurosurgery, Georgetown University School of Medicine.

Read before the Section on Nervous and Mental Diseases at the 104th Annual Meeting of the American Medical Association, Atlantic City, June 7, 1955. Also presented before the Neurosurgical Society of America, Pebble Beach, Calif., March 19, 1955.

* Reference 2. Bailey, P., in discussion on article by Gibbs, Gibbs, and Fuster.[20]

† References 6-8.

‡ References 10 and 11.

normal, but it had most likely been the factor which caused the generalized seizures. In this series one-half of the patients had excisions based on focal electroencephalographic changes only, without gross pathological changes being noted.

Sleep records were not acceptable in any patient in this series whose psychomotor seizures did not occur in sleep. Records were made and acceptable only within the parameters in which habitual psychomotor seizures occurred. Attention to fine details in the clinical history will provide the only methods of activation necessary. If seizures occur in early morning before breakfast, electrical recordings are best made during those hours. This is an extremely laborious method of study, but I believe it is necessary. The natural history of the disease fails to dictate that in most cases sleep or any artificial means of activation is a part of the psychomotor attack. Avoidance of sleep will eliminate a number of bilateral temporal foci. Furthermore, sleep gives inconsistent results, since at one time sleep is effective in producing the temporal spike focus, while at other times, in the same person, sleep is entirely noncontributory. Also, in certain persons, the whole brain does not fall asleep at the same time, so that an initial focus of slow waves will vary in different subjects. All this complicates the interpretation of sleep records, and if medicines are used to induce sleep the interpretation is further complicated.

There were 25 male and 11 female subjects, with ages ranging from 14 to 51 years. The indications for operation were (1) disability due to frequent and severe psychomotor seizures, in 15 cases, (2) disability due to psychomotor seizures, interseizure psychiatric disorder, and institutionalization, in 7 cases; (3) disability due to psychomotor seizures and interseizure psychiatric disorder, in 11 cases, (4) and disability due to psychomotor seizures and neoplasm, in 2 cases. One patient was operated on when his professional job was at stake because of frequent seizures, although he was not disabled. In all patients the seizures were uncontrolled after many years' use of anticonvulsant drugs. The duration of medical treatment for psychomotor seizures before operation averaged 14 years—6 years with adequate control and 8 years without adequate control. A complete outpatient and hospital neurological survey was made. This included (1) multiple electroencephalograms, demonstrating a consistent unilateral anterior temporal focus; (2) general and neurological history and examination; (3) blood serology and sugar, calcium, and phosphorus determinations; (4) spinal fluid examination; (5) pneumoencephalography; (6) bilateral closed arteriography, and (7) observation of psychomotor attack. Patients were selected for operation provided the electroencephalographic focus was consistently unilateral. If any lack of correlation between the side of the electroencephalographic focus and the results of the various objective tests was encountered, the patient was not considered for operation.

All operations with electrocorticograms were performed with use of local anesthesia without preoperative medication. In later cases general anesthesia with thiopental (Pentothal) sodium and endotracheal nitrous oxide was used, since electrical studies were not made.

Patients with uncontrolled, long-standing, frequent psychomotor seizures are pitiful, for their need of help is very great. The seizures, psychiatric disturbances, and intellectual deterioration contribute severely to their total disability. All this results in an intolerable social stigma. A promising operation should not be denied these people.

The "Standard" Operation

In the first 15 patients a frontotemporoparietal osteoplastic craniotomy, utilizing four burr holes, was made with the use of local anesthesia (Fig. 1). At the inferior and anterior margins of the craniotomy considerable bone was removed so as to expose the anterior middle fossa. One must gain access to the inferior surface of the temporal lobe with as little retraction as possible. The dura was opened, and the anterior temporal, inferior frontal, and inferior parietal areas were exposed. Superficial temporal, inferior frontal, and inferior parietal electrical recordings were made. Afterward, intratemporal recordings were made with a Grass depth electrode. The results of the electrical studies show, in general, that a spike focus was most consistently demonstrated approximately 4 cm. deep within the second temporal convolution. It resided in an area with its midpoint 4.5 cm. from the tip of the temporal lobe, as measured along the Sylvian fissure. When postage-stamp subdural electrodes were used, the discharge most commonly arose from the inferior and medial surfaces of the temporal lobe, being confined to an area approximately 2.5 cm. in

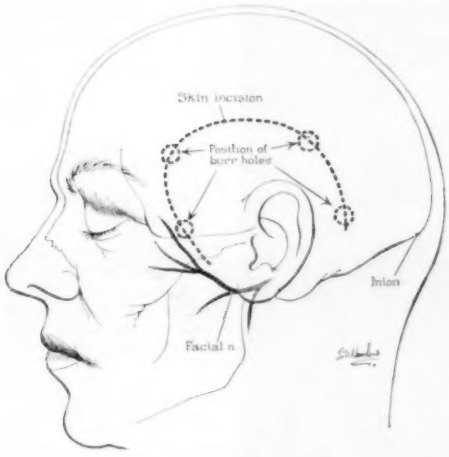


Fig. 1. — Frontotemporoparietal osteoplastic craniotomy ("standard" operation).

diameter. In other words, no discrete pinpoint focal discharge could be obtained from superficial or depth recordings. After repeated findings of this kind, electrical studies at operation were discontinued, and a "standard" lobectomy was used in 21 additional patients.

In the next 21 patients the operative approach was similar to that routinely used in the temporal approach for retrogasserian rhizotomy. The bony removal anteriorly, however, is much greater. The anterior 7 cm. of the temporal lobe can be exposed through this opening (Fig. 2). The anterior 6.5 cm. of the tip of the temporal lobe, as measured along the Sylvian fissure, is routinely removed. This removal included the uncus, the anterior 2-4 cm. of the hippocampal gyrus, the amygdala, and the anterior divisions of the first, second, and third temporal convolutions. The island of Reil was always exposed but never removed. After the removal is completed, one should visualize the middle cerebral artery, the lateral surface of the island of Reil, covered with piarachnoid, the opened tip of the temporal horn of the lateral ventricle, the posterior communicating artery, the anterior choroidal artery, the third nerve, the tentorial edge along the medial rim of the middle fossa, and, occasionally, the posterior cerebral artery (Figs. 3 and 4). Most frequently the anastomotic vein of Labbé was left intact; but when it occupied a position within the anterior 6.5 cm. of the temporal lobe, it was coagulated and partly removed. The descending horn of the lateral ventricle was always opened in order to identify the amygdala clearly. This mass was usually removed through a transventricular approach so that its removal could be complete from the visual anatomic standpoint. In removing the temporal tip by suction, care was always taken to avoid coagulation if possible, and hot moist packs and thorough irrigation were used freely. The subpial method of resection was always carefully employed so as to preserve normal circulation in the surrounding cortex. The wound was always thoroughly irrigated in order

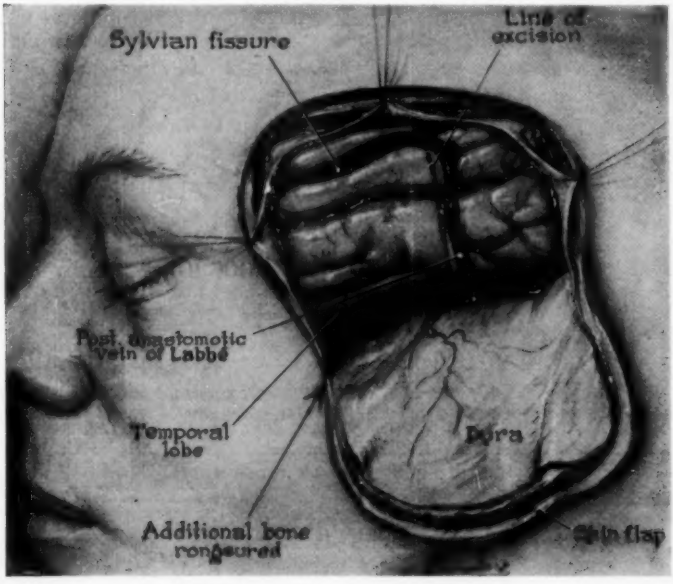


Fig. 2.—The anterior temporal lobe is exposed from the tip to beyond the vein of Labbé and from the Sylvian fissure to the floor of the middle fossa.

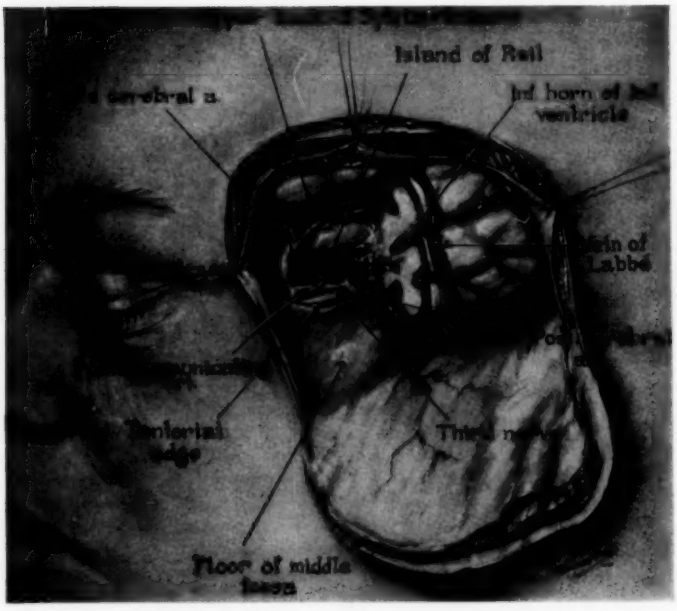


Fig. 3.—After removal of the anterior 6.5 cm. of the temporal lobe the island of Reil and adjacent structures are easily identified.

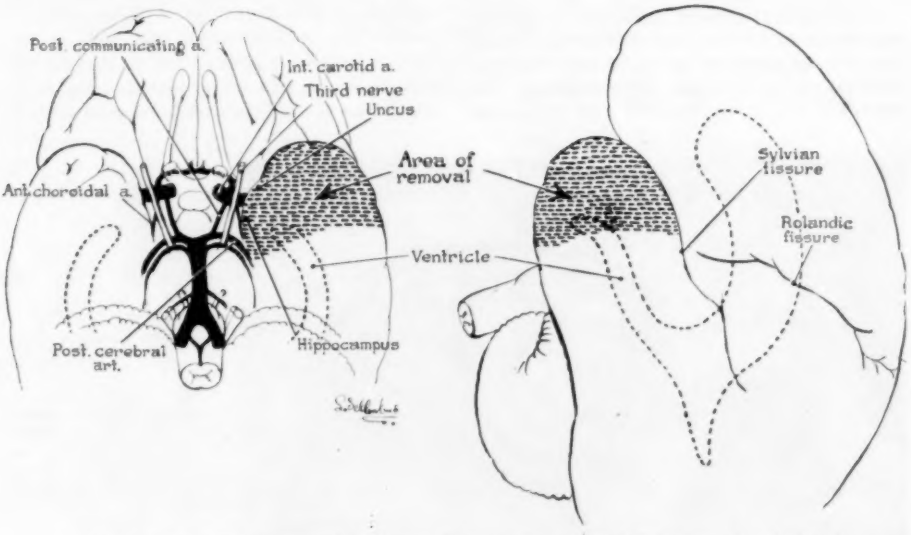


Fig. 4.—The area of removal is shown. Note that the ventricle is entered and that frequently one may visualize the posterior cerebral artery.

to obtain perfect hemostasis. The dura was always closed tightly, and the temporal muscle, fascia, and subcutaneous and cutaneous layers were closed with interrupted fine black nonabsorbable surgical (silk) sutures.

Effect of Operation upon Number of Seizures

Long-term operative results may be judged on two bases: (1) freedom from

psychomotor seizures only, and (2) freedom from all types of seizures. The latter method has been used by Penfield and Steelman.[9] I have prepared two tables so that both types of analysis may be studied (Tables 1 and 2). From the patient's standpoint the more worth-while analysis in this group is "freedom from psychomotor seizures only," since these were their disabling seizure type. The number of associated grand mal and/or petit mal seizures was never great enough to induce disability, for patients with this type were not selected for operation. Utilizing the latter classification (Table 1), one finds that 15 patients have had no attacks since leaving the hospital and an additional 12 patients are 75% improved or better. Thus, as judged at the end of a five-year average follow-up, a total of 75% have had successful operations. Two other patients have "fair results," and seven patients have little or no improvement. Judged in another way, 28 patients (78%) have been entirely free from psychomotor seizures since leaving the hospital. Three other patients are improved and five patients unimproved, but no patient is worse. Both analyses closely correlate the fact that, at present, 30 patients are economically independent, whereas all but one of these were disabled prior to operation (Table II). Over half the patients are also free from grand mal attacks. In contrast to the experience of Bailey and Gibbs,[2] only one patient has a greater number of grand mal attacks since operation. It is clear that

TABLE 1.—*Classification of Results Based on a Method of Analysis by Penfield and Steelman* (36 Patients)

Type of Attack	Group 4: No Attacks Since Leaving Hospital	Group 3: 75% Improved or Better	Group 2: 50% Improved	Group 1: 25% Improved	Group 0: No Improvement
Psychomotor seizures only	1(33.3%)	1(33.3%)	1(33.3%)		
Predominantly psychomotor with grand mal seizures	13(50%)	9(34.6%)	1(3.8%)	1(3.8%)	2(7.8%)
Predominantly psychomotor with grand mal and petit mal seizures	1(14.3%)	2(28.5%)		1(14.3%)	3(42.9%)
Total	15	12	2	2	5
	75% had successful operations		6% had "fair results"	19% had unsuccessful operations	

TABLE 2.—*Status of Thirty-Six Patients Four to Nine Years Following Operation*

Type of Attack	No. of Patients	No. of Patients Free from All Types of Seizures Since Operation	Average Time Elapsed Since Operation for All Patients
Psychomotor seizures only	3	1(33.3%)	4 yrs. 8 mo.
Predominantly psychomotor with grand mal seizures	26	13(50%)	5 yrs. 6 mo.
Predominantly psychomotor, with grand mal and petit mal seizures	7	1(14.3%)	4 yrs. 10 mo.
Total	36	15(41.7%)	5 yr.

when classical petit mal seizures occurred either in combination with psychomotor seizures or in combination with grand mal and psychomotor seizures, operation was successful in only two out of seven cases, so that I have come to look on the presence of classical petit mal seizures associated with bilaterally synchronous spike-and-wave 3-per-second electrographic activity as a contraindication to temporal lobectomy for the treatment of psychomotor seizures.

If one were to eliminate the patients with classical petit mal seizures from an operative category, one should be able to develop an operative success of approximately 83%.

Influence of Operative Type upon Results

Thirty-one patients had a "standard" unilateral operation. Three patients had unilateral bi-gyrectomy, and one patient had unilateral tri-gyrectomy. Only one of these four patients has obtained an excellent result, and that patient had a superficial astrocytoma in the first and second temporal convolutions. The patient with a bilateral temporal lobectomy has had 50% to 75% improvement in the number of attacks but is still disabled by his seizure problem. Thus, it is clear that almost all the good operative results have followed the more radical, but "standard," operation (Table 3).

Influence of Familial Neurological Disorders

When brain tumor is eliminated, the presence of neurological familial disorders limits considerably the likelihood of freedom from all seizures after operation. Yet there is just as much chance for a satisfactory result as was obtained in the total group. To counterbalance the initial statement, it may be stated that there is a chance for a greater improvement in psychiatric and social factors than was found in the total series. Definitely, then, the presence of neurological disorders in the family is not a contraindication to operation (Table 4).

Gross and Microscopic Pathological Changes

During operative inspection one-half of the patients showed gross pathological changes (Table 5). An absence of gross pathological findings did not lower the operative success. Thus, a well-demonstrated, consistently unilateral electroencephalographic anterior temporal focus is just as good an operative indication as a localized organic lesion in the anterior temporal region. One must think of focal physiological abnormalities in the same manner as one thinks of focal organic pathological lesions. They are both measurable, but the organic

TABLE 3.—*Influence of Type of Operation upon Operative Results*

Type of Operation	No. of Cases	Operative Results				
		No Improvement	25% to 50% Improvement	50% to 75% Improvement	75% to 95% Improvement	100% Improvement
Unilateral bi-Gyrectomy	3	1		1	1	
Unilateral tri-Gyrectomy	1					1
Unilateral anterior temporal lobectomy (includes uncus, amygdala, and hippocampus)	31	3		3	11	14
Bilateral temporal lobectomy	1			1		
Total	36	4		5	12	15

TABLE 4.—*Relationship of Neurological Disorders in the Family*

History of Neurological Disorder in the Family	No. of Patients	Results of Operation
Epilepsy	5	Only 2 had satisfactory operation; 1 has been free of all seizures for 5 yr.
Depressive psychosis	2	Both had satisfactory operation
Brain tumor	2	Both have been free from seizures
Migraine	2	One had no improvement; other had 75%-95% improvement
Total	11	Seven, had successful operations

lesion is more acceptable to most neurosurgeons.

Thickening of the meninges and avascular gyri were observed in one-third of the cases. Adhesions between the arachnoid and the dura, anterior temporal discoloration, atrophy of gyri, and small- to medium-sized softened areas were observed in approximately one-fourth of the cases. Focal areas of increased tenacity, vascular deformity, and congestion were observed in one out of six cases. A small anterior choroidal artery, a superficial cyst, a tumor without preoperative evidence of it, and a vascular malformation were among the uncommon findings at operation.

The tissues removed at operation were subjected to microscopic study in every case. The findings are tabulated in Table 6. The most marked changes were found in the uncus, closely followed by those in the hippocampal gyrus. Varied changes were also noted in all portions of the temporal lobe. However, microscopic changes were not observed in all cases. There were 17 cases in which microscopic changes were not noted, and the operative result in this group as compared with that in the group with microscopic changes was not appreciably different. Gliosis, increased satellitosis, shrinkage of nerve cells, neuronophagia, and other chronic degenerative changes were noted. Two astrocytomas were found at operation, and it is of considerable interest that there was no preoperative evidence of tumor. One of these tumors was entirely confined to the first temporal gyrus, the uncus, and the hippocampal gyrus. No microscopic evidence of tumor could be found in the second or third temporal gyrus. Four specimens from the island of Reil were available for study. Three of these specimens showed abnormal changes, whereas one was normal. In the specimen with the normal island of Reil the temporal lobe biopsy tissue was also normal. After lobectomy in this case the electroencephalographic spike focus was unaltered. A single undercut 1 cm. long in the island of Reil eliminated the spike focus. It has been five years since operation, and this patient has been free of all attacks with the exception of two minor ones. He is not taking any anticonvulsive medication, has subsequently

TABLE 5.—*Gross Pathological Changes Observed at Operation*

Gross Pathological Finding	No.
None	18
Thickening of meninges	12
Avascular gyri	11
Adhesions between arachnoid and dura	10
Anterior temporal discoloration	10
Atrophy of gyri	10
Softened areas	10
Focal areas of increased tenacity	7
Vascular deformity	6
Congestion	6
Small anterior choroidal artery	2
Cyst (superficial)	2
Tumor without preoperative evidence	2
Vascular malformation	1

TABLE 6.—*Microscopic Findings*

	1st Temporal Gyrus	2d Temporal Gyrus	3d Temporal Gyrus	Uncus	Hippocampal Gyrus	Island of Reil
Astrogliosis	12	11	13	19	16	3
Shrinkage	12	12	14	18	15	3
Neuronophagia	11	11	13	17	15	2
Satellitosis	13	14	15	19	17	2
Chronic degenerative changes	11	10	14	18	16	2
Demyelination	10	9	12	16	12	1
Apparent loss in capillaries	6	5	6	11	9	1
Meningeal thickening	10	10	10	16	14	4
Astrocytoma (cystic)	1	1	1	1	1	?
Astrocytoma (piloid)	1	0	0	1	1	?
Apparent increase in vascularity	4	5	4	5	5	0
Numerous corpora amylacea	2	3	2	4	4	0
Totals	93	91	104	145	125	18

Amygdala not satisfactory for analysis owing to suction method of removal.

become a rabbi in an effort to discharge his gratitude, and is happily married.

Relationship Between Side of EEG Focus and Operative Result

The left, or dominant, side was resected in three-fourths of the patients. This suggests that left temporal lobe lesions induce greater disabilities. I cannot recall ever seeing a patient with psychomotor epilepsy who was left-handed and who had a right temporal lobe focus. The dominant lobe being more fully developed, it may have a more complicated effect on behavior and psychiatric patterns, since these factors are closely allied to psychomotor seizures. Yet the improvement in behavior and psychiatric patterns is just as great when the nondominant temporal lobe is removed (Fig. 5).

Relationship of Aura and EEG Focus to Operative Result

The commonest aura was related to the epigastrium (Table 7). The majority of the group with an aura of this type demonstrated deep unilateral anterior temporal electrical foci after the patients had been free of medication for five or more days. Sixty-six per cent of these patients have been free from all types of seizures since operation, whereas only 41.7% of the entire series could be classified similarly. Thus, an epigastric aura with a deep unilateral anterior temporal electrical focus definitely increases the likelihood of an excellent operative result. This finding is especially interesting, since the epigastric aura has often carried the stigma of idiopathic epilepsy rather than of temporal epilepsy. One should not deduce, on the other hand, that every patient with a convulsive seizure problem who has an epigastric aura either will show a temporal focus or will profit from a temporal lobectomy. However, the absence of an aura does not argue against a worth-while result, since two-thirds of this group obtained a satisfactory result, although they are not free from all seizures. One patient, disabled by frequent daytime psychomotor and grand mal seizures, has suffered with only rare nocturnal grand mal fits and is entirely economically independent.

Déjà vu occurred in five patients, and three have been entirely free from all seizures since lobectomy. Other aurae are tabulated in Table 7. When focal motor seizures accompanied the epigastric, visual, somatosensory, or forced thought aura, the result was excellent in five of six cases.

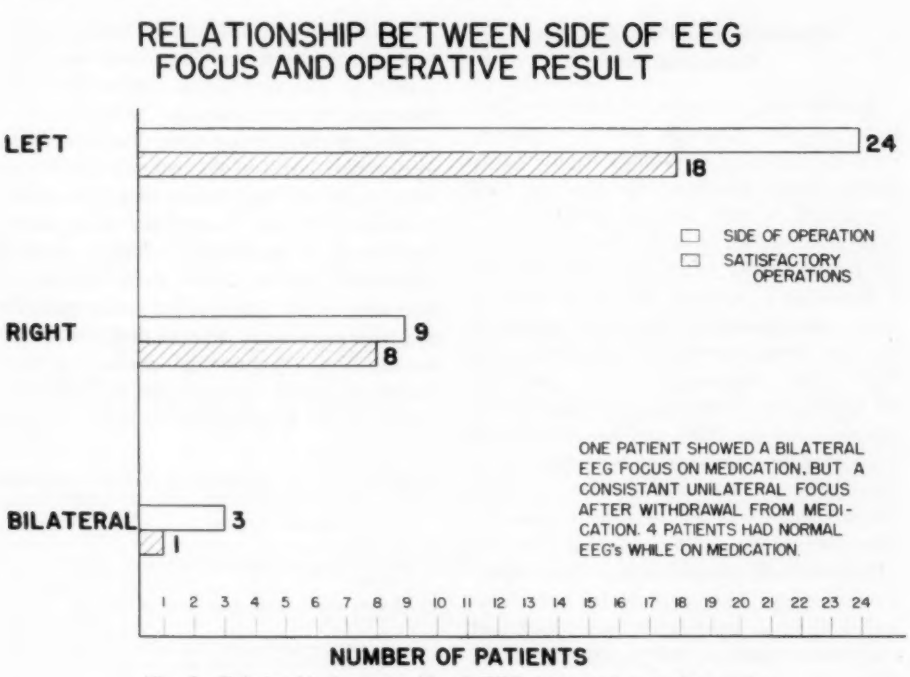


Fig. 5.—Relationship between side of EEG focus and operative results.

TABLE 7.—*Relationship of Aura, EEG Focus, and Operative Result*

No. of Patients	Type of Aura	Site of EEG Focus	Operative Results
8	Gastric or epigastric only	5-Deep temporal anteriorly 1-Diffuse temporal 1-Posterior temporal 1-Anterior but superficial	Excellent, all 5 Poor Poor Satisfactory
1	Epigastric or feeling of fright	Anterior and superficial	Satisfactory
1	Epigastric or déjà vu	Deep anterior temporal	Excellent
1	Epigastric, cephalic, or dizziness	Deep anterior temporal	Excellent
5	Deja vu	All had deep foci except one, whose focus was superficial	Excellent, 3 Satisfactory, 1 Poor, 1
2	Fear	One with superficial and 1 with deep anterior temporal	Excellent, 1 Satisfactory, 1
6	None	3 with deep and 3 with superficial anterior temporal	Satisfactory, 4 50% Better, 1 Not improved, 1
3	Forced thinking	All with deep anterior temporal foci	Excellent, 1 75% improved, 2
2	Confusion	All with deep anterior temporal foci	Excellent, 1 Poor, 1
1	Motor eye movements	Deep anterior temporal	50%-75% improvement
2	Motor Aphasia	Deep anterior temporal	Both with satisfactory results
1	Olfactory	Deep anterior temporal	Satisfactory
1	Visual	Deep anterior temporal	Excellent
1	Tingling of hand	Deep anterior temporal	Excellent
1	Cephalic	Deep anterior temporal	Satisfactory

Operative and Postoperative Complications

In obtaining access to the lowermost portions of the temporal lobe for inferior temporal electrical recordings, a minor peripheral facial weakness occurred in eight cases, and in each case complete recovery took place within 6 to 12 months. One of my most grateful patients is a man who had a hemiplegia without facial involvement occur approximately six hours following recovery from anesthesia. This patient has made a 90% recovery, has been free from all attacks for seven years, has subsequently married, has one child, and has worked and supported his family since operation. There have been no operative deaths. In three patients there was an increase in abnormal behavior, which rapidly subsided after the withdrawal of phenacemide (Phenurone). These patients had unsuccessful operations, and additional medication was instituted. One other patient had weakness of the right side of the face and right arm and hand, with a minor motor aphasia. There was complete recovery of speech in three months, and three and a half years later there was a 90% recovery of motor function. During the interim he was not disabled and worked as a painter. One other patient was said to have developed postoperative osteomyelitis of the bone flap, which necessitated removal and subsequent tantalum cranioplasty elsewhere. His result from the initial procedure has been excellent, and no convulsive seizures have occurred in the five years and three months since operation. One patient subsequently had a reactivation of an acute paranoid schizophrenic condition and has required institutionalization for the past five years. A pathological survey of the tissue removed revealed diffuse cerebral changes suggestive of Pick's atrophy. There was no relief from seizures.

Medical Treatment Before and After Operation

The patients had received an average of 14 years of medical treatment before operation was performed. The group was subjected to an average of eight years of treatment, without adequate control.

Medical therapy has been discontinued in almost one-fourth of the patients for at least two years and not more than six years. One-third of the group have been maintained on a markedly reduced medical regimen (i. e., less than three-fourths of the preoperative dose). Ten other patients are taking the same dose as they took prior to operation. Only five patients have greater dosage schedules since operation (Table 8). Since all the unsuccessful operative results

TABLE 8.—*Use of Medicines Following Operation*

Medical Therapy	No.	
Patients whose medicines are markedly reduced	13	58.3%
Patients entirely without all medicines from 1-5 yr.	8	
Patients taking same amount of medicine as they required preoperatively	10	
Patients who have taken a greater dose of medicines since operation	5	

are in the last two categories, it appears that medical treatment does not alter the operative analysis. In several cases there was a temptation to increase the dose of anticonvulsant medicines, but this was avoided so that the postoperative analysis would not be complicated. It is quite clear that after operation a lower anticonvulsant dosage accomplished a greater control in all but five patients. Even though one does not obtain an "excellent" operative result, many patients and their referring physicians will be grateful for the improved response to medication.

Ten patients developed psychomotor status epilepticus before operation, after sudden withdrawal of medication in the hospital. One patient had 10 to 12 attacks daily; he became maniacal, and one university hospital demanded his discharge. When he was transferred to another university hospital, his study had to be carried out on the locked wards. Another patient, who had 8 to 10

attacks daily, was confused the entire day, and could not recall her name, date, birth, or the place she lived.

If one were to reason that 18% of the operative group who are free from psychomotor seizures are free because of improved medical treatment, the operative success would be reduced by only 10%. Thus, 68%, instead of 78%, would be free of seizures as a result, most likely, of operation. The 18% has been taken from studies by McNaughton.[11]

Relationship Between Psychiatric Disorder and Operative Results

The majority of patients with psychomotor seizures have mild or severe personality changes (Table 9). When severe personality changes are present, the chances are about even that a seizure-free result will be obtained, as well as an improvement in personality. When mild personality changes are present, there are 9 chances out of 10 that the patient will have a successful operation. The duration of the seizure problem is not directly related to the severity of personality change. However, a study of the case histories of some of the patients suggests that if operation had been performed earlier the chance for success would most likely have been greater. Of psychotic patients whose psychoses were unclassified, only 60% had a worth-while operation, but in some instances remarkable reversals of personality changes were rated as more beneficial to the patient than was relief from psychomotor seizures. Five patients had schizophrenia, and it is significant that, although the operation furnishes useful value in controlling psychomotor attacks, there is a poor over-all operative result. Of the six cases of manic-depressive states, all but one has had more than 75% improvement since operation, and there has been a remarkable relief from the depression. Mania and its allied reactions are also easily controlled. Hallucinations were present in three patients, and two of these have been entirely free from hallucinations and all forms of seizures

TABLE 9.—*Relationship Between Psychiatric Disorder and Operative Result*

Psychiatric Disorder*	No. of Patients	Results of Operation†	Comment
Severe personality changes	14	Satisfactory, 5 Fair, 4 Poor, 4 Excellent, 1	Changes are about even that, other things being equal, a satisfactory result will be obtained, with personality improvement
Mild personality changes	10	Satisfactory, 5 Excellent, 4 Poor, 1	90% of this group had a successful operation
Unclassified psychosis	8	Satisfactory, 3 Fair, 2 Poor, 3	Only 60% had worth-while operation
Schizophrenia	5	Satisfactory, 1 Fair, 1 Poor, 3	Operation has useful value in controlling psychomotor attacks but furnishes poor over-all results
Manic-depressive state	6	Excellent, 1 Satisfactory, 4 Poor, 1	All but one is more than 75% improved since operation, with marked relief from depression
Hallucinations	3	Excellent, 2 Poor, 1	Two have been entirely free from hallucinations and all forms of seizures; 1 is unchanged and is institutionalized
Hysterical personality	1	Poor	Slightly below normal intelligence with no change in seizures or personality
Mental retardation	2	Excellent, 1 Fair, 1	Operation provided 1 patient with freedom from seizures for 7 yr.; in other case family notes operation worth-while after 3 yr.

*A patient may be listed under several classifications. For example; one schizophrenic with hallucinations was listed under "Schizophrenia" and "Hallucinations."

†Excellent means complete freedom from seizures plus decided favorable change in psychiatric disorder; satisfactory, 75% improvement in all seizures and psychiatric disorder; fair, 50% improvement in all seizures and psychiatric disorder; poor, less than 50% improvement in all seizures and psychiatric disorder.

since operation. However, one patient has had no effect on his seizure problem and remains institutionalized, with chronic hallucinations. This patient had a bilateral temporal lobectomy, which included bilateral removal of the amygdaloid nucleus. One patient with a hysterical personality had a poor operative result, with no change in seizures or personality. Two mentally retarded patients came to operation. One of these patients presents the oldest postoperative result (nine years) and has been entirely free from seizures. The family is well pleased with the operative result, and they constantly write me of their gratitude. The other patient has only a fair result, is disabled, and is economically dependent (Table 9).

Many abnormal psychiatric and social factors were improved after operation. These have been tabulated in Table 10. The most marked improvement was noted in mood, independence, tolerance of people, depression, increased interest in job, irritability, activity, worry, and social contact. Initiative, behavior, and memory were improved in three-fourths of the patients. It was interesting that judgment, evaluation, perception, insight, and calculation, although improved in a high percentage of patients, were lowest in factors analyzed. These latter factors, often referred to as functions of the temporal lobe, are noted as being least improved. It is therefore clear that from this type of change following operation patients are more socially acceptable and have a better chance of increasing their job rating. At present all but seven of these patients are working and are economically independent (Table 11).

It is evident that temporal lobectomy, in psychomotor epileptics, will remove or substantially change cerebral interconnections so that the final psychiatric effect is of decided benefit to the patient. This is also a common observation in the well-controlled nonoperative patient. One patient who had daily feelings of wanting to kill her mother has been free of these disturbances since operation. Five patients have had no im-

TABLE 10.—*Relation of Psychiatric and Social Factors and Operative Results*

Psychiatric and Social Variations	Patients Given Normal Scores Before Operation By Examiner	Patients with 75%-95% Improvement Since Operation	Percentage Increase Toward Normal Since Operation
Mood	4	25	625
Dependence upon others	4	24	600
Tolerance of others	4	23	575
Depression	4	21	525
Interest in job	5	23	460
Irritability	6	24	400
Activity	7	27	385
Worry	5	19	380
Sociability	7	25	358
Initiative	8	27	337
Behavior	8	27	337
Memory	8	23	287
Judgment	10	26	260
Evaluation	11	27	245
Perception	10	24	240
Insight	12	26	217
Calculation	16	26	163
General appearance	19	30	158

TABLE 11.—*Status of Patients Four to Nine Years After Unilateral Temporal Lobectomy for Psychomotor Seizures*

Type of Attack	No. of Patients		Employed		Keeping House	Dependent and at Home	Institutionalized
	Males	Females	Fully	Partly			
Psychomotor seizures only	2	1	1	1	1		
Predominantly psychomotor with grand mal seizures	18	8	19	1	2	2	2
Predominantly psychomotor with grand mal and petit mal seizures	4	3	3		2*		2
Total	24	12	23	2	5	2	4
	36		30 Economically independent			6 Fully dependent	

* One patient died four years after operation with eclampsia, two weeks following childbirth.

provement in personality, and none of this group has a successful operation with respect to eliminating the seizures. Another patient, who made four attempts at suicide in six preoperative months, has been free from seizures, is economically independent, married, and has been adjusted for six and a half years.

Memory changes contribute to a satisfactory postoperative result. One patient, a physician's former secretary, did not recall her wedding 16 years previously. Now, six years since operation, she is free from seizures, has returned to her job, and recalls her wedding and its associated events. Seizures were so frequent in another patient that his conversation was not intelligible and his memory suffered severely. In the four postoperative years, seizures have been rare, occurring only in sleep; his memory is excellent, and he has established an electrical service company.

There are 15 patients who exhibited progressive mental deterioration for years before operation and in whom there has been an arrest of this process since operation. For five of this group operation was not successful in elimination of seizures. The electroencephalogram has improved in each of these patients.

Economic Status of Patients Three to Eight Years After Operation

Many types of analysis are applicable to postoperative studies, but the most practical analysis is one concerning the economic ability of the patient to function in normal life and to retain his economic independence for a long period. In this group, of 24 male and 12 female patients, 23 are fully employed and 2 are partly employed. Five are keeping house, making a total of 30 patients who are economically independent (Table 11). Six patients are fully dependent, four being institutionalized. The completely disabled man with predominantly psychomotor seizures and with grand mal seizures has proved the one who most likely will work and fully support his family after operation. The presence of petit mal seizures lessens the likelihood of a good postoperative work record. All patients are living except one. This patient had psychomotor, grand mal, and petit mal seizures and a poor postoperative result. She died four years after operation, with eclampsia two weeks following childbirth.

One-half of the patients with economic independence work as laborers, in clerical jobs, or as housewives. One patient, formerly institutionalized for six years, has

been free of seizures for three years, is a licensed electrician, has worked regularly for five years, and fully supports himself. Another patient, a long-term dependent upon his family, his self-supporting and fully employed as an aircraft architect. One patient with a poor result is working at a better job because all of his attacks have been nocturnal during his five postoperative years.

Freedom from the disabling forms of seizures, economic independence, and disturbing psychiatric complaints offers the greatest postoperative benefit in terms of practical living. If these factors are considered in summation, 66% of the patients have successful operative results (Table 12).

TABLE 12.—*Postoperative Results in Terms of Practical Living*

Type of Analysis Applied to Group	Results in 36 Patients	
Freedom from all types of seizures	41.7%	66% of patients had successful operations when all practical factors have been totally evaluated
Freedom from psychomotor seizures only	78 %	
Freedom from grand mal seizures only	58 %	
Freedom from economic dependence	85.7%	
Freedom from disturbing psychiatric complaints	66.6%	

Comment

The "standard" operation used in this series is quite different from that used by others.[2] The anterior 6.5 cm. of the tip of one temporal lobe is routinely removed. This includes the first, second, and third convolutions; the uncus; the hippocampal gyrus, and the amygdaloid nucleus. Emphasis is placed on removal of the last three structures. This removal can be made on either side without inducing a neurological clinical sign or a psychiatric behavorial or personality change. At operation electrical studies show that the focus resides in an area about the uncus, the anterior hippocampus, and the amygdaloid nucleus. Restricted procedures in the temporal lobe when automatism is the major concern has been successful in only one of four cases.

I have selected the method of Penfield and Steelman[9] (Table 1) to analyze the cases, but I have subdivided the classification to show that there were three patients with psychomotor seizures only, and that the majority had predominantly psychomotor and grand mal attacks. Clinical petit mal attacks associated with primary bilateral synchronous 3-cps wave-and-spike activity is rarely affected by temporal lobectomy, for the disturbance is probably a primary condition of the centrencephalic system. Yet the fact that one patient is free from attacks and two others are 75% improved or better suggests that the anterior temporal areas removed have some influence on centrencephalic function. This has been well demonstrated by a number of stimulation experiments.§

The presence of epilepsy in the family reduces the likelihood for freedom from seizures but does not reduce the chance for a worth-while operative result. Genetic epileptic influence usually implies a primary centrencephalic disorder. When this exists, the areas removed must function as an entry into the mechanism involved. Presumably this takes place largely by way of the amygdaloid connections with the brain stem.

Excision of electrographic lesions is not a new concept, for this has been emphasized repeatedly where there is an associated organic lesion.‖ However, in the absence of organic changes, excisions of electrographic foci have not been thoroughly studied. One-half of the patients had no gross pathological changes, and only one of this group showed microscopic alterations. Thus, there were 17 patients who had

§ References 15, 16, and 17.

‖ References 10 and 11.

excisions based primarily upon electroencephalographic evidence. Results in this group are not appreciably different in regard to the number of seizures. However, this group enjoys a slightly better psychiatric and social status, possibly because of the absence of brain damage to other parts. All this supports the idea that certain alterations in the electroencephalographic pattern are quite helpful in assigning a proper diagnosis to any form of intermittent behavorial or seizure state.¶ It is proper to think of focal physiological lesions in the same manner as one thinks of focal pathological lesions.

The epigastric aura has had favorable reclassification in the past 10 years. Patients having some form of epigastric aura constitute the most successful operative group. The chance to obtain freedom from all types of seizures is increased by 25%. Such relationships imply that the epigastric aura arises from the anterior temporal area and should no longer be a signal to classify the attack as "idiopathic."

All but six patients have some type of aura. In this small group without aurae no one is free from seizures, although four have a satisfactory result. The differentiation of a case with automatism due to an ictal centrencephalic discharge and one due to a cortical discharge probably depends on the presence of an aura in the latter case. Differentiation can prove very difficult, but clinical observation of attacks and prolonged electrical studies will add further knowledge. One must remember that bilateral rhythms occur quickly, often with little evidence of lateral temporal surface discharge. It follows, then, that any evidence of an aura should arouse suspicion of a focal, temporal, pathological, or electrical lesion.

One may consider that electrical discharges are capable of operating in the hippocampus without a discernible alteration of neocortical activity. This is clearly observed in animals,# and I believe I have observed it in man. It is conceivable that frequent discharges of this kind may alter the patient's ability to form permanent memory mechanisms. In other words, there are many subclinical psychomotor seizures which produce a profound accumulative adverse effect on memory. If so, removal of this structure could improve memory mechanisms. This may explain the favorable alterations in memory following an excellent operative result.

That psychomotor fits can occur in the absence of the uncus, hippocampus, and amygdaloid nucleus is evidenced by four unsuccessful cases in this series. Penfield has also demonstrated this in a patient who had these structures removed for attacks of automatism without relief from attacks. Four years later removal of the remaining hippocampal gyrus, insular cortex, and all of the auditory cortex resulted in a relief of automatism.[11] Automatism also continued in one patient after bilateral temporal lobectomy.

Severe personality, mental, and transient psychotic states are common in patients having uncontrolled psychomotor seizures. This state is favorably altered by temporal lobectomy. The favorable response is sometimes of more practical advantage than freedom from psychomotor seizures. This accounts for the higher rating by the patient and the family than by the surgeon. There is no difference in the outcome in the presence or in the absence of a pathological lesion. I have not observed a postoperative complication of behavior, mental, or personality state, except in three cases in which it was due to phenacemide and in one case in which an acute paranoid condition was reactivated.

Automatism may occur, without convulsive attack, from a discharge of the "centrencephalic" system. In this case 4- to 6-cps, bilaterally synchronous rhythms can be recorded. I have excluded all such cases from operation. Practically all cases

¶ References 2 and 19.

References 15 and 16.

with automatism will show (*a*) bilaterally synchronous 3-cps wave-and-spike activity; (*b*) anterior temporal spike, sharp wave, or slow wave, and (*c*) bilaterally synchronous 4- to 6-cps waves. It would seem that there are several ganglionic mechanisms to explain automatism.

It is evident that the anterior temporal region in psychomotor epileptics is concerned with mood, depressive reaction, interest, memory, sociability, initiative, behavior, judgment, insight, and other factors, for these factors are greatly changed by operation (Table 5). However, this conclusion is not a totally valid one, for freedom from seizure produces an influential state on general well-being.

The psychomotor state, or automatism, is truly a seizure. It is not akin to the "automatism" which follows convulsive seizures, since the former occurs at a higher organizational level. The latter is more akin to confusion. Hughlings Jackson's doctor with psychomotor seizures did solve complicated problems during the seizure,[17] but I do not believe he could have done it during the "automatism" which follows a convulsive seizure.

The psychomotor seizure of focal temporal origin can easily be recognized in most cases by the presence of an aura plus some of the common behavioral findings listed in Table 13. Amnesia is an essential component, but the duration is of less importance.

It is reasonable that focal seizures should become a problem of the neurosurgeon, for, as McNaughton has pointed out, they constitute the poorest results from medical therapy.[11] This is truest of the focal temporal group. In 18% there were one or more attacks per week, while in only another 18% no attacks or rare small attacks in one year.

Many bilaterally synchronous rhythms disappear after temporal lobectomy, indicating the ability of the temporal lobe to activate the centrencephalic system or to function as an integral anatomic part of this system. Thus, many patients with bilateral synchronous seizure discharges, formerly rejected from operation, may actually be good candidates. Bilateral lobectomy may be beneficial to selected bitemporal seizure problems. The only true electroencephalographic pattern of "idiopathic" epilepsy is the spike and dome of petit mal epilepsy. All other bilateral syn-

TABLE 13.—*Behavioral Findings Associated with Psychomotor Seizures*

Behavioral Findings	No. of Times Observed	Behavioral Findings	No. of Times Observed
Incoordination	26	Screaming	8
Confusion	25	Running	7
Staring	20	Pushing	6
Negativism	18	Rubbing	5
Searching	17	Laughing	4
Swallowing	17	Plucking	4
Confused talking	17	Rage	4
Does not answer	15	Appearance of daydreaming	4
Fumbling with environment	15	Crying	3
Groping	12	Throwing objects	2
Smacking lips	12	Spitting	2
Chewing	11	Singing	2
Walks without incoordination	10	Whistled in church	1
Undressing	9	Stealing	1
Shouting	9		

chronous rhythms should be suspected of arising from unilateral focal regions. Dependence upon the pneumoencephalogram and arteriogram to demonstrate an organic change in structure must be abandoned, for only 36% showed changes in either of these studies that lateralized the lesion. All of us are familiar with unbelievably large intracranial masses without pneumoencephalographic or arteriographic changes.

One must not assign all importance to freedom from seizures. Psychiatric and social disturbances were so often improved that the patient and his family would rate the success of the operation higher than the surgeon's independent rating. This improvement makes for easier acceptance into society and increases the job rating. Schizophrenics with psychomotor seizures do not make good candidates for operation. Although the seizures may be controlled, the lack of change in schizophrenic behavior minimizes the favorable effects on the number of seizures. Hallucinations have been eliminated by unilateral temporal lobectomy in nonpsychotic patients who have psychomotor seizures. However, one schizophrenic patient with psychomotor seizures and hallucinations is unchanged after bilateral temporal lobectomy (including removal of both amygdaloid nuclei). This observation would suggest that the mechanism of hallucinations is different in psychomotor epilepsy and in psychosis.

The economic status of a previously long-term dependent group of patients is of practical importance. The economically dependent person who after operation attains his economic independence also attains added psychiatric and social advantages. One advantage kindles another, so that favorable adjustment to life situations of stress is found. At the time of writing, 30 of 36 patients have economic independence.

Summary

A completely disabled patient with medically uncontrolled psychomotor seizures who shows a consistent unilateral electrical focus in the anterior temporal region has a 41% chance of being free from all seizures for five years after temporal lobectomy. There is a 78% chance of being free from psychomotor seizures, a 58% chance of being free from grand mal seizures only, a 66% chance of attaining freedom from disturbing psychiatric complaints, and an 86% chance of gaining economic independence. In summation, two of three patients will gain a successful operation when all practical factors have been totally evaluated. This compares favorably with results in many other neurosurgical procedures employed today. These deductions are based on the results in 36 patients who have been followed for an average of five years since one anterior temporal lobe was removed. It is essential that the removal include not only the temporal tip but also the uncus, the hippocampal gyrus, and the amygdaloid nucleus.

REFERENCES

1. Morris, A. A.: The Surgical Treatment of Psychomotor Epilepsy, M. Ann. District of Columbia 19:121-131, 1950.

2. Bailey, P., and Gibbs, F. A.: The Surgical Treatment of Psychomotor Epilepsy. J. A. M. A. 145:365-370, 1951.

3. Green, R., Jr.; Duisberg, R. E. H., and McGrath, W. B.: Focal Epilepsy of Psychomotor Type: A Preliminary Report of Observations on Effects of Surgical Therapy, J. Neurosurg. 8:157-172, 1951.

4. Bailey, P.; Green, J. R.; Amador, L., and Gibbs, F. A.: Treatment of Psychomotor States by Anterior Temporal Lobectomy, A. Res. Nerv. & Ment. Dis. Proc. (1951) 31:341-346, 1953.

5. Obrador, S.: Personal Experiences in Surgical Treatment of Epilepsy, J. Neurosurg. 10:52-63, 1953.

6. Guillaume, J.; Mazars, G., and Mazars, Y.: Surgical Indications in So-Called Temporal Epilepsy, Rev. neurol. 88:461-501, 1953.

7. Petit-Dutaillis, D.; Christophe, J.; Pertuiset, B., and Dreyfus-Brisac, C.: Semaine hôp. Paris 29:3838-3847 (Dec. 2) 1953.

8. Bailey, P.: Observations on Surgical Treatment of Psychomotor Epilepsy, Zentralbl. Neurochir. 14:195-206, 1954.

9. Penfield, W., and Steelman, H.: The Treatment of Focal Epilepsy by Cortical Excision, Ann. Surg. 126:740-762, 1947.

10. Penfield, W., and Erickson, T.: Epilepsy

and Cerebral Localization, Springfield, Ill., Charles C Thomas, Publisher, 1941.

11. Penfield, W., and Jasper, H.: Epilepsy and the Functional Anatomy of the Human Brain, Boston, Little, Brown & Company, 1954.

12. Penfield, W., and Baldwin, M.: Temporal Lobe Seizures and the Technique of Subtotal Temporal Lobectomy, Ann. Surg. 136:625-634, 1952.

13. Gibbs, E. L.; Gibbs, F. A., and Fuster, B.: Psychomotor Epilepsy, Arch. Neurol. & Psychiat. 60:331-339, 1948.

14. Pope, A.; Morris, A. A.; Jasper, H.; Elliott, K. A. C., and Penfield, W.: Histochemical and Action Potential Studies on Epileptogenic Areas of Cerebral Cortex in Man and the Monkey, A. Res. Nerv. & Ment. Dis. 26:218-233, 1946.

15. MacLean, P.: The Limbic System and Its Hippocampal Formation, J. Neurosurg. 11:29-44, 1954.

16. Kaada, B. R.: Somato-Motor, Autonomic and Electrocorticographic Responses to Electrical Stimulation of Rhinencephalic and Other Structures in Primates, Cat and Dog, Acta. physiol. scandinav. (Supp. 83) 24:1, 1951.

17. Jackson, I. H.: Selected Writings of John Hughlings Jackson: I. Epilepsy and Epileptiform Convulsions, edited by J. Taylor, London, Hodder & Stoughton, 1931.

18. Jasper, H. H.; Ajmone-Marsan, C., and Stoll, J., Corticofugal Projections to the Brain Stem, A. M. A. Arch. Neurol & Psychiat. 67:155-166, 1952.

19. Gastaut, H.: The Epilepsies, American Lecture Series, Springfield, Ill., Charles C Thomas, Publisher, 1954.

20. Gibbs, F. A.; Gibbs, E., and Fuster, B.: Anterior Temporal Localization of Sleep-Induced Seizure Discharges of Psychomotor Type, Tr. Am. Neurol. A. 72:181-182, 1947.

Guillain-Barré Syndrome and Presumed Allergic Purpura

L. M. SANGHVI, M.R.C.P. (London), D.T.M.H. (England)
and
R. SHARMA, M.D., Jaipur, India

That the Guillain-Barré syndrome may, at least in some instances, be a manifestation of hypersensitivity has been suggested by several writers.* Association of this syndrome and other clinical manifestations of hypersensitivity has been reported in cases following administration of serum and typhoid-paratyphoid (T.A.B.) vaccine.† The case to be described exhibited nonthrombocytopenic purpura, arthritis, and edema in association with the syndrome following upon a streptococcal skin infection. To our knowledge it appears to be the first instance of this nature.

Report of a Case

A married, well-built, well-nourished housewife, aged 41, was admitted to the hospital on Nov. 7, 1955, with complaints of shooting pains in all four limbs and marked weakness, pain in the joints, edema of the face and arms, and extensive subcutaneous hemorrhages. The illness had started on Oct. 5, 1955, with slight swelling and pain in the joints and puffiness of the face and arms. A week later pain developed in the muscles of the upper limbs, with marked weakness. By Oct. 16 the lower limbs were also involved. On Nov. 1 she had severe shooting pains in the limbs, which she described as electric currents. Owing to increase in muscular weakness, she could not move her limbs at all and became confined to bed. On Nov. 3 she noticed red areas of varying size under the skin. These soon became extensive and covered the limbs.

She gave a history of having had an urticarial eruption for three days five years previously and of similar attacks off and on for six months two years before admission. During the preceding year, off and on, she had had pustular eruption on the left leg. She denied having had any injection of serum or vaccine or blood transfusion.

On admission the patient looked very ill, and was in agony due to the severity of pain in the limbs. She was apprehensive and afraid of the slightest movement or touch, which was extremely painful. The temperature was normal, the pulse 120 and respirations 20 per minute, and the blood pressure 150/100 mm. Hg. There was some puffiness of the face and slight edema of the arms, as well as swelling of the ankle, knee, and wrist joints. Extensive ecchymoses and purpuric spots practically covered the limbs, and a few pustules were present on the left leg. Neurological examination revealed normal intelligence, speech, cerebral functions, and cranial nerves. There were flaccid paralysis of all muscles of the extremities, most marked distally; slight wasting of the forearm, hand, and leg muscles, and marked muscular tenderness. The biceps, triceps, knee, and ankle jerks were absent, and the abdominal reflexes and plantar responses were normal. There were marked hyperesthesia of the skin of the soles and impairment of superficial sensations and vibration sense below the middle of the thighs and arms. The optic discs were slightly congested.

Laboratory examination showed a total leucocyte count of 29,000 per cubic millimeter, with 80% polymorphonuclear cells and 20% lymphocytes; red cells 4,500,000 per cubic millimeter; hemoglobin 14.5 gm. per 100 cc.; a negative Kahn test; normal platelet count and bleeding and clotting times, and an erythrocyte sedimentation rate of 68 mm. in one hour. Cerebrospinal fluid examination showed a protein content of 180 mg. per 100 cc. on Nov. 8, of 130 mg. on Dec. 1, and of 100 mg. on Dec. 12, with normal cell counts. The total leucocyte count gradually decreased to 26,000 on Nov. 11, to 18,200 on Nov. 18, and to 9,200 on Dec. 29. The E.S.R. on Dec. 29, was 15 mm. in one hour. Smear from a pustule showed streptococci.

Therapy consisted of penicillin, thiamine and ascorbic acid, acetylsalicylic acid, antihistaminics, and, later, physical therapy and cyanocobalamin (vitamin B_{12}). Ten days after admission the shoot-

Recorded for publication April 6, 1956.

Department of Medicine, S.M.S. Medical College.

* References 2, 9, 12-14, 16.

† References 8, 9, 13.

ing pains had ceased. There was gradual, though very slow, improvement in muscle power, and by Dec. 15 she could walk with support. She was then given prednisolone (Deltacortril) 20 mg. orally daily for three weeks beginning Dec. 24, without any apparent hastening of the recovery. At the time of discharge from the hospital, on Jan. 30, there was only slight residual weakness. The hemorrhages were gradually absorbed.

Comment

The Guillain-Barré syndrome, of polyradiculoneuritis with albuminocytological dissociation, has been known to follow a variety of infections, bacterial and viral, but all attempts to identify an etiologic infectious agent have proved unsuccessful.[6] The syndrome has sometimes followed parenteral introduction of foreign proteins into the body after immunization procedures or blood transfusion. It has been reported to follow successive normal parturitions.[14] Search for a pathogenic factor in these cases suggests an allergic antigen-antibody reaction as the common denominator. There are grounds for this allergic theory, though they cannot be considered conclusive. The uniform latent period following infections and inoculations is not inconsistent with the period required for the development of a hypersensitivity state. Occurrence of the syndrome after serum sickness also suggests relationship to such a state. The outstanding histopathological changes in autopsied cases of the Guillain-Barré syndrome are pronounced swelling and edema of the nerve fibers.[15] Edema of various tissues is common in serum disease. It is now generally agreed that this edematous response, in this syndrome and other neurological complications developing after serum administration, may represent an allergic response of the central nervous system similar to the edematous reactions in the skin. Since skin and nerve tissue are both ectodermal in origin, they might be expected to react similarly. Miller and Stanton,[9] reviewing the literature concerning the neurological complications of serum injection and prophylactic inoculation, suggested that the common factor in the pathogenesis of the encephalitic, myelitic, Landry, Guillain-Barré, radicular, polyneuritic, and mononeuritic syndromes was anaphylactic hypersensitivity. Sanghvi and Gupta[14] suggested that all neurological syndromes of hypersensitivity be grouped together under a common title of "disseminated hypersensitization neuropathy." Finally, the concept of allergy has led to the trial of corticotropin and cortisone in the treatment of the Guillain-Barré syndrome, and experience so far indicates that they are of value in reversing the course of illness in many cases,‡ thereby providing therapeutic support for this concept.

Reitman,[13] in a review of literature, could find only two cases, in addition to one of his own, which fulfilled the criteria of the Guillain-Barré syndrome and which were associated with manifestations of serum sickness. Miller and Stanton,[9] in their review of cases following typhoid-paratyphoid vaccine inoculation, mention that a local reaction at the site of injection is common, whereas a generalized urticaria appears to be rare. Association of allergic manifestations and the syndrome after bacterial infection does not appear to have been reported. The case reported here, with signs and symptoms of polyradiculoneuritis and albuminocytological dissociation, can be classified as fulfilling the criteria of the Guillain-Barré syndrome and illustrates the occurrence of the syndrome in association with purpura of Schönlein's type, following upon streptococcal skin infection. This type of purpura accompanied by a normal platelet count has been attributed to specific allergens.§

This association of allergy-like manifestations with Guillain-Barré syndrome provides support for the theory that an antigen-antibody reaction is the chief mechanism underlying the Guillain-Barré syndrome.

Summary

Association of purpura with the Guillain-Barré syndrome is reported. This associa-

‡ References 1, 4, 5, 10, 11, 16, 17.

§ References 3 and 7.

tion supports the theory that an allergic reaction is the underlying pathogenic factor of the Guillain-Barré syndrome.

Dr. L. R. Sarin, Superintendent, S. M. S. Hospital, permitted the publication of this case.

REFERENCES

1. Blood, A.; Locke, W., and Carabasi, R.: Guillain-Barré Syndrome Treated with Corticotrophin (ACTH), J.A.M.A. 152:139-140 (May 9) 1953.

2. Brain, W. R.: Diseases of Nervous System, Ed. 3, New York, Oxford University Press, 1947, pp. 795-798.

3. Clement, D. H., and Diamond, L. K.: Purpura in Infants and Children: Its Natural History, A. M. A. Am. J. Dis. Child. 85:259-278 (March) 1953.

4. Crozier, R. E., and Ainley, A. B.: Guillain-Barré Syndrome, New England J. Med. 252:83-88 (Jan. 20) 1955.

5. Fiese, M. J.; Cheu, S., and Radding, J.: Guillain-Barré Syndrome in Infectious Mononucleosis: Report of a Case with Recovery Following Administration of Cortisone, A. M. A. Arch. Int. Med. 92:438-441 (Sept.) 1953.

6. Haymaker, W., and Kernohan, J. W.: Landry-Guillain-Barré Syndrome: Clinicopathological Report of 50 Fatal Cases and a Critique of the Literature, Medicine 28:59-141 (Feb.) 1949.

7. Gairdner, D.: The Schönlein-Henoch Syndrome (Anaphylactoid Purpura), Quart. J. Med. 17:95-122 (April) 1948.

8. Kamman, G. R., and Weisberg, M.: Polyneuritis with Facial Diplegia (Neuronitis) Following Serum Sickness in Adult, Minnesota Med. 23: 789-791 (Nov.) 1940.

9. Miller, H. J., and Stanton, J. B.: Neurological Sequelae of Prophylactic Inoculation, Quart. J. Med. 23:1-27 (Jan.) 1954.

10. Newey, J. A., and Lubin, R. I.: Corticotropin (ACTH) Therapy in Guillain-Barré Syndrome, J. A. M. A. 152:137-139 (May 9) 1953.

11. Plum, F.: Multiple Symmetrical Polyneuropathy Treated with Cortisone, Neurology 3:661-667 (Sept.) 1953.

12. Pullen, R. L., and Sodeman, W. A.: Infections Polyneuritis (Guillain-Barré Syndrome), Am. J. M. Sc. 211:110-122 (Jan.) 1946.

13. Reitman, N., and Rothschild, K.: Non-Infectious Nature of Guillain-Barré Syndrome with Possible Explanation of Albumino-Cytologic Dissociation, Ann. Int. Med. 32:923-934 (May) 1950.

14. Sanghvi, L. M., and Gupta, K. D.: Disseminated Hypersensitisation Neuropathy, Indian M. Gaz. 89:484-491 (Aug.) 1954.

15. Scheinker, I. M.: Pathology and Pathogenesis of Infectious Polyneuritis (Guillain-Barré Syndrome), J. Neuropath. & Exper. Neurol. 8:184-193 (April) 1949.

16. Seltzer, H. S.; Lichty, D. E., and Conn, J. W.: Case of Guillain-Barré Syndrome (Infectious Polyneuritis) with Apparent Response to ACTH, Univ. Michigan M. Bull. 18:27-31 (Jan.) 1952.

17. Stillman, J. S., and Ganong, W. F.: Guillain-Barré Syndrome: Report of a Case Treated with ACTH and Cortisone, New England J. Med. 246: 293-296 (Feb. 21) 1952.

Effects of Chlorpromazine on Chronic Lobotomized Schizophrenic Patients

A Controlled Study

HARRY FREEMAN, M.D.
and
HERBERT S. CLINE, M.D., Worcester, Mass.

There have been numerous articles attesting to the therapeutic efficiency of chlorpromazine in psychoses. There has also been a notable dearth of controlled studies utilizing placeboes to evaluate the role of the enthusiasm of the psychiatrist, the ward personnel, and the patients themselves. A search of the literature has noted only two, those of Gardner, Hawkins, Judah, and Murphree [1] and of Kovitz, Carter, and Addison,[2] both dealing with chronic schizophrenic patients.

The present study is of the double-blind variety, in which the effects of chlorpromazine and placeboes on two matched groups of chronic schizophrenic patients were noted. It was not intended, primarily, as a therapeutic investigation but was organized to determine the threshold dose of the drug which would produce an effect distinguishable from that obtained on administering placeboes.

Method and Material

The technique used in evaluating the status of the patients was as follows: After an interview, a modification of the Malamud-Sands Rating Scale[3]—15 items—was scored to determine the effects upon various phases of the clinical picture. This scale is shown in Table 1. The deviation from the normal in each item is rated on a six-point scale on either side of the base line and a total score obtained by the addition of the numbers for each item. The first seven items can be observed directly, and the next eight can be determined from the responses during the interview. In a general way, the gradations on the left represent those attitudes which are directed away from the subject, and those on the right indicate internally directed forms of behavior. The higher the score, the more abnormal is the clinical status of the subject. The chief value of the rating is that it represents an attempt to quantify changes in the various elements in the behavior of the patients over the period of the study.

The subjects of the investigation were chronically disturbed schizophrenic patients on whom lobotomies had been performed after failure of all previous therapies. There were 20 male patients, divided into two groups and matched primarily on the basis of means of the rating scores and secondarily on the basis of age, duration of hospitalization, and years since lobotomy. One group was given placebos and the other group chlorpromazine, but the identity of the medication was unknown to the psychiatrist doing the ratings (H. S. C.), the ward personnel, and the patients. The medication was given solely by mouth and twice daily, in individual envelopes, so that the identity and the dosage of the tablets was known only to one of us (H. F.). The placebos, of course, had an appearance identical with that of the drug.

Results

The results of the study are shown in Figure 1. Here are depicted the mean scores for the placebo and chlorpromazine groups in successive weeks. The chlorpromazine was administered in a dosage noted at the bottom of the Figure, 200 mg. daily for the first four weeks, 400 mg. daily for the next two weeks, 600 mg. daily for the next two weeks, 800 mg. daily for the next three weeks, and then placeboes for the next four weeks.

The mean scores show a sudden drop in the first week of treatment, then a variable

Received for publication Jan. 9, 1955.

Dementia Praecox Research Project, Department of Mental Health, Worcester State Hospital.

TABLE 1.—*Psychiatric Rating Scale*

Function	6	5	4	3	2	1	Base Line	1	2	3	4	5
Appearance	Bizarre		Decorative		Overmeticulous			Slovenly	Untidy	Incontinent	Smearing	
Motor activity	Excited		Agitated		Restless			Underactive	Retarded		Stuporous	
Mimetic expression	Incongruous		Dramatizing		Exaggerated			Stiff	Waxy flexibility		Mask-like	
Responsivity	Anaclitic		Suggestible		Dependent			Stubborn	Resistive		Negativistic	
Hostility reactions	Destructive		Combative		Belligerent			Self-deprecating	Self-mutilating		Suicidal	
Socialization	Disruptive		Meddlesome		Outreaching			Shut-in	Isolated		Inaccessible	
Attention	Uncontrolled		Markedly distractible		Moderately distractible			Preoccupied	Disparative		Completely withdrawn	
Speech	Incessantly productive		Push-of-speech		Overtalkative			Undertalkative	Retarded	Blocking	Mute	
Mood	Exhilarated		Euphoric		Enthusiastic			Somber	Despondent		Deeply depressed	
Affect	Inappropriate		Explosive		Labile			Inadequate	Bland		Flat (rigid)	
Feeling	Panic		Anxious	Tense	Supersensitive			Phlegmatic	Dull		Apathetic	
Perception	Hallucinations		Illusions; pseudo-hallucinations		Exaggerated intensity			Self-observation	Hypochondriasis	Conversions	Somatic hallucinations	
Thought processes	Fragmented		Alogical; paralogical		Illogical			Rationalizing	Obsessive hair-splitting		Obsessive doubt	
Subjective reorganization	Cosmic (omnipotence)	Delusions	Delusion of grandeur	Ideas of persistence	Ideas of inference	Ideas of reference		Ideas of inferiority	Self-accusatory	Somatic delusions	Nihilistic	
Insight	Negation of problem		Probably exogenous	Recognition of probability without concern	Shifting of blame			Self-hypercritical	Add. of nonexisting problems	Despairing self-blame	Attitude of complete helplessness	

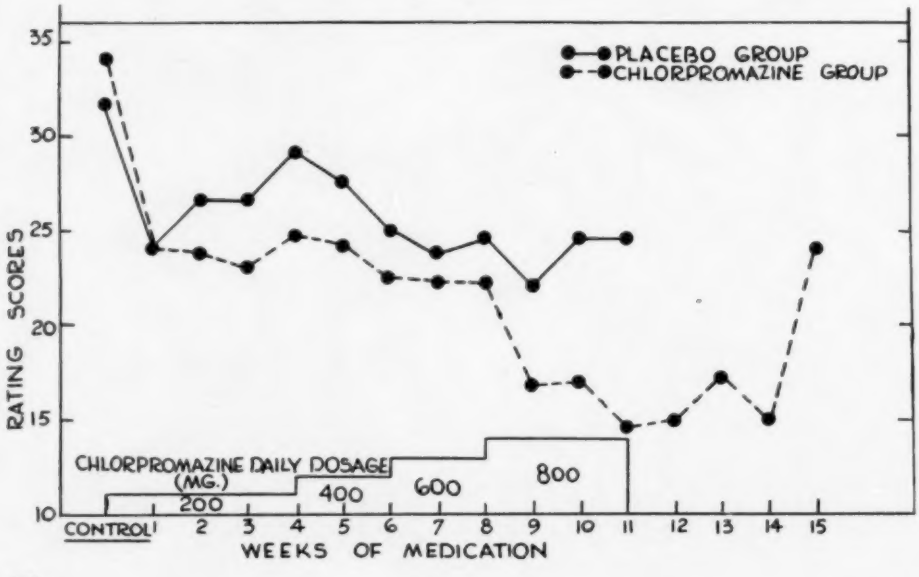
TABLE 2.—*Means and Ranges of Variables Used in Matching Patients in Placebo* and Chlorpromazine* Groups*

	Placebo		Chlorpromazine	
	Mean	Range	Mean	Range
Chronological age	36.3	23-49	38.4	30-57
Years in hospital	11.2	4-27	9.4	4-17
Years postlobotomy	7.5	1-16	8.2	1-13
Pretreatment rating score	31.4	19-38	34.0	27-48

* Ten patients each.

degree of fluctuation over the next seven weeks, but no consistent change. It was for this reason that the dosage was varied. It was not until the dosage had been increased to 800 mg. daily that the chlorpromazine group showed a decrease in its mean score. This was noted within a week and continued to drop irregularly in the next two weeks. It is evident, then, that for this group of patients the threshold dosage lay between 600-800 mg. daily. At the end of three weeks of medication at this level of dosage, the patients who were taking chlorpromazine were given placeboes. For three weeks there was no essential change in the mean score, but during the fourth week the score rose again above the level noted preceding the 800 mg. dosage period. It is apparent that the "tranquilizing" effect of the drug lasts between three and four weeks after the medication is omitted.

There are several points of interest in this trend which may be described in more detail. Initially, the chlorpromazine group had a slightly, but not significantly, higher score than the placebo group. This was due primarily to the fact that the ratings for "motor activity," "appearance," "affect," and "subjective reorganization" (delusions) were higher. During the first week of the study the scores dropped in both groups, but in the chlorpromazine-treated patients there was a greater fall in these same items, so that the mean scores for the first week of medication were the same. The decrease in scoring may be primarily due to the enthusiastic hopefulness of both the psychiatric personnel and the patients at the onset of a new therapeutic study, so that the patient-doctor rapport was increased and the abnormal phenomena either seemed not so abnormal or were less obviously displayed. Certainly, the gross scores per subject



showed a lessening in 9 of the 10 patients in each group, indicating a universality of operating factors.

Following the initial drop in scores there is a secondary rise which reaches its maximum in the fourth week of the study and which is more marked in the placebo-treated group. This increase was present in six of the nine patients in each group. The other patients in each group showed a decrease. The distribution of trends for each group was the same, but one of the chlorpromazine-treated patients (on a dosage of 200 mg. daily) showed such a marked decrease in scores as almost to offset the increases in the six.

The reason for the increase in scoring is obscure. The patients were living on three different wards, an equal number from each group on each ward. It would, therefore, be unlikely that some factor common to the hospital environment would affect patients on different wards. It is also difficult to presume that an endogenous variability would affect 12 out of the total group of patients simultaneously. It would seem more likely that the variable factor may be the judgment of the psychiatrist.

At any rate, the general level of scores for each group was essentially the same from the first to the eighth week of medication, so that we may conclude that the dosage of chlorpromazine up to this point was not sufficient to affect the group as a whole. At a dosage of 800 mg. of chlorpromazine, the values for the two groups differentiate.

The data have been analyzed to determine the significance of the difference between the two trends. In order to include the variation observed previously and achieve a more reliable base line, for each subject the sum of the scores obtained during the three weeks before the 800 mg. daily dosage was introduced (weeks 6 to 8) was compared with the sum of the scores obtained during the three weeks on the 800 mg. daily dosage. The difference between the two sums was computed for each subject. The values are seen in Table 3. For the placebo-treated group the median value for the three pre-800-mg. weeks was 76.5; for the chlorpromazine-treated group, 71.0. There is no statistically significant difference between

TABLE 3.—*Sums of Scores in Placebo-Treated and Chlorpromazine-Treated Groups for the Three Weeks Before the 800 Mg. Daily Dosage Was Begun and Differences Between These Sums and Those Obtained During the Three Weeks at a Daily Dosage of 800 mg.*

Placebo Group			Chlorpromazine Group		
Subject No.	Sum of Scores Before 800 Mg. Dosage	Difference in Sums of Scores Under 800 Mg. Dosage*	Subject No.	Sum of Scores Before 800 Mg. Dosage	Difference in Sums of Scores Under 800 Mg. Dosage*
1	83	−13	1	54	0
2	37	−13	2	87	0
3	58	− 6	3	28	+8
4	107	− 1	4	87	+18
5	43	0	5	50	+20
6	78	+ 2	6	48	+20
7	75	+ 8	7	88	+23
8	89	+ 8	8	73	+25
9	97	+19	9	70	+34
10	68	+21	10	76	+40
Median	76.5	1.0†		71.5	20.0†

* Plus signs indicate improvement in score.
† Difference between corresponding values for chlorpromazine and placebo groups is statistically significant. $P=0.02$ by Mann-Whitney U-test.

the two figures. The median difference * between these values and the sum of the scores obtained in the 800 mg. daily dose period was +1 for the placebo group and +20.0 for the chlorpromazine group. The differences between these values is statistically significant, the probability being 0.02. This difference between the two groups of patients is not affected by the initially higher values for the placebo-treated group because (*a*) there was no significant difference between the pre-800-mg. dose values in the two groups; (*b*) there was no relationship between the initial levels and the shift in values during the 800 mg. daily dose period. It should be noted at this point that this statistical technique is conservative, since it takes into account the trend before the medication has achieved its maximum effect at the end of the three-week peeriod of medication at the 800 mg. dose.

As the medication, at what we consider an adequate dosage, was given for only a short period of time, a therapeutic judgment would not be very valid but is given for what it is worth. On the basis of the rating scale, in the placebo group, seven showed no improvement and three showed a mild degree of improvement. Of the chlorpromazine group, five showed a mild improvement and five showed a moderate degree of improvement, the latter referring purely to better hospital adjustment. One patient in each group was in seclusion throughout the whole study, and each showed a similar degree of mild improvement. In view of the similarity of numbers in each group showing a slight change, it should probably be considered that this level of improvement in drug-treated patients should be attributed to the altered environmental situation.

Four of the chlorpromazine-treated group showed an improvement in their scores before the 800 mg. daily dosage level was reached. Two had shown a mild improvement, one at the 400 mg. dosage level and one at the 600 mg. dosage level, with no further improvement at the larger dosage levels. Two had shown a moderate degree of improvement, one at 200 mg., with no further improvement, and one at 400 mg., with further improvement at the 800 mg. dose.

In order to determine what elements of the rating scale changed during this period of maximum dosage, we have used the same technique as that for the individual total scores, namely, to add the scores for each item before the 800 mg. dosage was instituted and compare it with the ratings during the three weeks this dosage level was maintained. The results are shown in Table 4.

In the placebo-treated group, none of the changes were significantly different from one another, indicating a completely random variation. For the chlorpromazine-treated group, there were eight items that showed significant trends from their base line in the direction of improvement (positive changes)—mimetic expression, responsivity, hostility reactions, socialization, speech, feeling, perception, and thought processes. However, if the variation in the placebo group is taken into consideration, significant differences are found in only four—responsivity, socialization, perception, and thought processes. Again, it should be noted that this technique is conservative in that it takes into account the improvement before the maximum has been reached, thus diminishing the magnitude of the trends. At any rate, it is encouraging that in these chronic, lobotomized schizophrenic patients there is improvement not only in interpersonal relationships (as shown by the first two items) but also in the intrinsic psychotic processes in so far as this can be detected in the psychiatric interview.

As has been noted in Figure 1, once the medication has been omitted, there is a reversion to a previous score, or even above it, between the third and fourth weeks. The individual scores showed this "rebound" in all the subjects, although three of the five patients who had previously shown a moderate degree of improvement clinically

* Positive changes indicate improvement in the score.

TABLE 4.—*Changes in Ratings for Individual Items in the Three Weeks Before the 800 Mg. Dosage of Chlorpromazine Was Begun as Compared with Changes for the Three Weeks During the 800 Mg. Daily Dosage, with Comparison of these Changes in the Two Groups*

Item	Chlorpromazine		Placebo		Chlorpromazine *vs.* Placebo, *P* Value
	Change	*P* Value	Change	*P* Valve	
Appearance	10	----	8	----	----
Motor activity	−2	----	0	----	----
Mimetic expression	19*	0.05	2	----	0.10
Responsivity	22*	0.02	0	----	0.05†
Hostility reactions	17*	0.05	0	----	----
Socialization	18*	0.01	3	----	0.05†
Attention	13	----	2	----	----
Speech	10*	0.05-0.02	7	----	----
Mood	0	----	−3	----	----
Affect	4	----	−1	----	----
Feeling	10*	0.05-0.02	−2	----	0.07
Perception	13*	0.02	0	----	0.05†
Thought processes	28*	0.001	−2	----	0.05†
Subjective reorganization	10	----	−5	----	----
Insight	15	----	4	----	----

* Difference between sums of rating scores for individual items for three weeks before 800 mg. dose of chlorpromazine is instituted and those obtained during the three weeks at the 800 mg. dose is statistically significant by Wilcoxon's test for paired replicates.

† Difference between corresponding values in individual items for chlorpromazine-and placebo-treated groups is statistically significant by the Mann-Whitney U-test.[4]

maintained this level during the period in which the chlorpromazine was omitted. A study of the individual items shows this same trend. In Figure 2 is shown a comparison of the changes in the items while the patient was taking chlorpromazine (800 mg. daily dose); (week 8-week 11) with those after omission of the drug for four weeks (week 11-week 15). On the left is shown the decrease in values under this dosage; on the right, the increases after omission. It may be seen that, with the exception of "speech" and "attention," all the items on the right changed about as much as or more (in the opposite direction) than the ones on the left. The most striking reversals are seen for "subjective reorganization" (delusions), "affect," "perception" (hallucinations), "motor activity," and "hostility reactions." Thus, in both thinking processes and ward behavior the patient reverted to his previous behavioral characteristics, evidence of a merely suppressive effect of the drug.

So far as untoward effects were concerned, no serious ones were noted in this small group. Complete blood counts, taken every two weeks throughout the study, showed no consistent change. Three patients showed some degree of unsteadiness, one of whom exhibited a mask-like facies. These patients had shown only a slight improvement, while the five who were moderately improved showed no abnormal symptoms. Thus, there seemed to be no relationship between clinical improvement and drug toxicity. Withdrawal of the drug resulted in a prompt disappearance of such symptoms.

It was previously mentioned that in four patients improvement in the rating scale was evident at lower doses than 800 mg. The reason for this is unknown. There was no relationship between the threshold dosage and age, duration of hospitalization, years since lobotomy, or the clinical status as evidenced by the rating score.

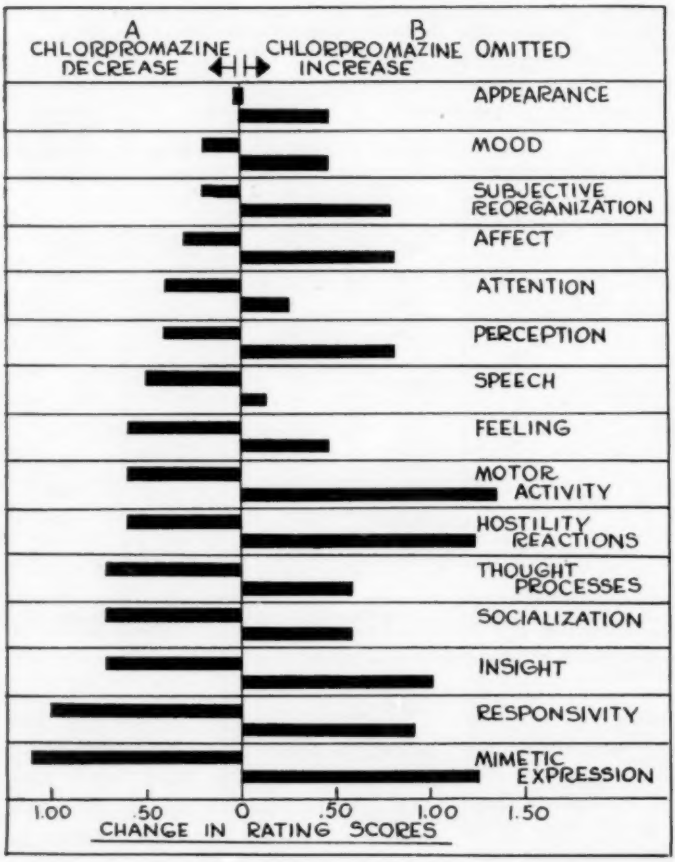


Fig. 2.—Changes in mean rating scores for each item (*A*) during chlorpromazine therapy (800 mg. daily for three weeks), and (*B*) during omission of chlorpromazine for four weeks.

Comment

It is evident from the trend over the 11-week period that the administration of any substance, no matter how innocuous, coupled with the inevitable increased attention, results in some degree of improvement in behavior even in long-institutionalized schizophrenic patients. Such improvement is evident early and soon reaches a limit. A drug demonstrates its potency only when its therapeutic results exceed the point attained by the placebo situation. For this reason, "slight" or "mild" degrees of improvement should be questioned as being solely due to pharmacological effects of the medication.

In this study the effective oral dose of chlorpromazine has been found to be between 600 and 800 mg. daily. This amount is somewhat higher than those used in the other controlled studies with a chronic schizophrenic population, one [1] at 100-400 mg. and the other [2] at 500 mg., but is far lower than that employed in some therapeutic studies, e. g., Kinross-Wright,[5] in which the average dose was 2400 mg. It may well be that had the lower dosage levels been maintained for a longer time than two weeks a change in the rating scale would have been noted. On the other hand, 9 of the 10 patients showed changes in the rating scale within one to two weeks after the institution of a given level of dosage, so that on the basis of consistency it would seem that the results obtained were valid.

The reasons for the wide variation in therapeutic dosages are obscure.

The rapid onset of changes in behavior at this level of dosage (within a week) and the duration of effects once the medication was discontinued (four weeks) suggest that the maintenance dosage may be intermittent rather than constant, with a consequent economic saving and a minimizing of complications.

The most encouraging result of this study was the significant improvement in thought processes and the reduction in hallucinations. For this to occur in chronic psychotic patients argues for a better prognostic outlook than has hitherto been considered possible with any other form of therapy.

Summary

Twenty male lobotomized schizophrenics, who had been hospitalized an average of 10 years, were divided into two groups matched for age, duration of hospitalization, years since lobotomy, and psychiatric status (Malamud-Sands Rating Scale). One group was given placeboes and the other chlorpromazine by mouth, on a double-blind basis. When the chlorpromazine dose was increased to 800 mg. daily, the scores on the rating scales for the two groups were differentiated, the placebo group showing little or no change, whereas the chlorpromazine group showed a significant trend to betterment in their scores. An analysis of 15 items which were used in the rating scale showed that on 4—responsivity, socialization, perception (hallucinations), and thought processes—the improvement in the chlorpromazine group was statistically significant.

Dr. John E. Lane assisted in the statistical analysis, and Smith, Kline & French Laboratories supplied the chlorpromazine and placebo tablets.

REFERENCES

1. Gardner, M. J.; Hawkins, H. M.; Judah, L. N., and Murphree, O. D.: Objective Measurement of Psychiatric Changes Produced by Chlorpromazine and Reserpine in Chronic Schizophrenia, Psychiat. Res. Rep. 1:77-83, 1955.

2. Kovitz, B.; Carter, J. T., and Addison, W. P.: A Comparison of Chlorpromazine and Reserpine in Chronic Psychosis, A. M. A. Arch. Neurol. & Psychiat. 74:467-471 (Nov.) 1955.

3. Malamud, W., and Sands, S. L.: A Revision of the Psychiatric Rating Scale, Am. J. Psychiat. 104:231-237 (Oct.) 1947.

4. Walker, H. M., and Lev, J.: Statistical Inference, New York, Henry Holt & Co., Inc., 1953.

5. Kinross-Wright, V.: The Intensive Chlorpromazine Treatment of Schizophrenia, Psychiat. Res. Rep. 1:53-62, 1955.

Obituaries

ROBERT PAUL BING, M.D.
1878-1956

Robert Bing's death brings to an end the career of one of Europe's most illustrious neurologists and severs one of the last golden links with the past. Neurology was Bing's obsession. Taking neurological meetings seriously, he could always be found, in and out of the lecture hall, scribbling notes for inclusion in a new edition of one of his books. Then he would return to his commodious bachelor quarters, lined by shelves of books which reached to the ceiling, to transcribe his new extracts into more usable form. He was a devotee of eponyms, for to him the names of neurologists had personal, if not historical, significance. To Greek also he was addicted. He coined such words as "erythroprosopalgia" and "anisosthenia," which usually fell on deaf ears. Once he wrote to a colleague: "There is no doubt that 'hemifacial atrophy' is better because more logical than 'facial hemiatrophy,' though the adjective 'hemifacial' as a Helleno-Latin hybrid—like a lot of medical terms—could provoke philological criticism."

ROBERT PAUL BING, M.D.
1878-1956

Bing could express himself vigorously, and often did, as in answer to the query put to him whether the chapter on aphasia in his "Kompendium" should not be modified: "Now, as you know, the question of aphasia is the battlefield of divergent opinions. In the U.S.A. the 'noëtic' school (with Kurt Goldstein as its most conspicuous representative) has numerous adherents who try to prove that aphasic syndromes are not essentially due to lesions of localized cerebral foci, but to more or less generalized psychic deterioration. I need not say that this

point of view is irreconcilable with the doctrines of aphasia proposed by myself as well as by Dejerine, Liepmann, Oppenheim, James Purves-Stewart, Walshe, Lotmar, Isserlin, Alajouanine, Mingazzini, Henschen and the immense majority of neurological clinicians—at least in Europe."

Bing was the kind of man who preferred the quiet of his study. He could enjoy an hour with a musician, a painter, a man of letters, a general, or a big dealer in peanuts, but after that he had to have his rest. His mother figured very strongly in his life. On Jan. 15, 1951, he wrote me, then in nearby Neustadt: "Profoundly distressed by the sudden passing away of my mother (aged 94, the last of my near relatives), and needing absolute rest after this severe shock, I do not feel able to receive you at this time. Rest is very necessary to me anyway."

Bing is best known for his "Kompendium." This small volume, dealing with the principles of localization of lesions in the nervous system, appeared in German in 1909 and saw fourteen editions. It found its way into seven other languages—French, English, Spanish, Polish, Hungarian, Greek, and Russian. In the earlier days practically every American neurologist cut his teeth on this book. A man always alert for a pointed story, Bing liked to tell how he happened one day upon a Russian version of his "Kompendium," published without his consent, in a bookstall in Basel. The next day he asked a Russian acquaintance, "And how is it that in Russia a book can be translated without permission of the author?" The Russian replied, "When someone translates the Bible, does he have to get permission from God?"

Robert Bing was born in Strasbourg on Aug. 5, 1878, and some years later moved with his family to Basel. Accorded the M.D. degree in 1901 by the University of Basel, he took a three-year (1902-1905) *Studienaufenthalt,* during which he worked with Munk in Berlin, Horsley in London, Babinski and Dejerine in Paris, and Edinger in Frankfurt am Main. Back in Basel, he became the leading spirit in a campaign to have clinical neurology recognized as a specialty in Switzerland. By 1907 he established, at his own expense, a neurological dispensary (*Nervenambulatorium*) and continued to support it without outside financial assistance for forty-seven years, when its doors were finally closed (1954). In 1918 he joined with others in founding the Swiss Neurological Society and was its president from 1919 to 1922. From 1919 onward he was editor of the *Schweizer Archiv für Neurologie und Psychiatrie.* He became *Extraordinarius* to the University in 1918, but not until 1932 was he made *persönlicher Ordinarius,* which carried appointment to the chair of neurology in the University, the first in Switzerland. He was elected vice-president of the International Neurological Congress in Bern in 1931, received an honorary degree from the University of Liége, was elected *Ritter* in the French Legion of Merit, and was made honorary member of several national academies and associations. Despite all this recognition, Bing remained a modest man. Once asked to prepare a preface for a colleague's book, Bing replied: "He has overwhelmed my work and my person with so much panegyrical praise and eulogy that I feel obliged to avoid everything calling forth the *'Société d'admiration mutuelle.'*"

Bing's contribution to neurology was enormous. He was author of some 200 articles, including chapters for several *Handbücher,* and, perhaps most important of all, he guided about 250 students in the preparation of their dissertations.

In 1952, the medical faculty of Basel renewed his medical diploma, issued to him 50 years previously, and paid tribute to his pioneering work in neurology.

About March 1, 1956, he delivered the concluding lecture of the winter semester. A colleague described it as "a vigorous lecture, still abounding with those refreshing ideas which for a half-century had brought graduates in neurology to him from all corners of the earth." Two weeks later, on March 15, 1956, he died, of a sudden heart attack.

Bing was once asked to name the 15 publications from his own hand of which he was fondest. They follow:

Über angeborene Muskeldefekte, Arch. path. Anat. 170:175, 1902.

Anatomie und Entwicklungsgeschichte des Gehirns von Ceratodus Fonteri, in Zoologische Forschungsreisen in Australien und dem malayische Archipel, edited by Richard Semon, Jena, G. Fischer, 1904, Vol. IV, p. 513.

Beitrag zur Kenntniss des endogenen Rückenmarksfasern beim Menschen, Arch. Psychiat. 39:74, 1904.

Eine kombinierte Form der heredofamiliären Nervenkrankheiten, Deutsches Arch. klin. Med. 83:199, 1905.

Myopathia rachitica, Jahrb. Kinderh. 68:649, 1908.

Die Bedeutung der spino-cerebellaren Systeme, Wiesbaden, J. F. Bergmann, 1909.

Über alkoholistische Muskelveränderungen, Med. Klin. 5:613, 1909.

Gehirn und Auge, Ed. 2, Munich, J. F. Bergmann, 1923.

Hyperkinésies organiques et psychogenes, Schweiz. Arch. Neurol. u. Psychiat. 18:163, 1926.

(with B. Walthard) Quelques aspects anatomo-pathologiques de la myélite herpétique expérimentale, Schweiz. Arch. Neurol. u. Psychiat. 22:3, 1928.

Die multiple Sklerose, Basel, Benno Schwabe & Co., 1932.

Das Prinzip der "Enthemmung" in der Physiopathologie, Schweiz. Arch. Neurol. u. Psychiat. 32:177, 1933.

Somatische Faktoren in der Gestaltung psychogener Symptome, Schweiz. med. Wchnschr. 66:953, 1936.

Lehrbuch der Nervenkrankheiten, Ed. 8, Basel, Benno Schwabe & Co., 1947.

Kompendium der topischen Gehirn- und Rückenmarksdiagnostik, Ed. 14, Basel, Benno Schwabe & Co., 1953.

WEBB HAYMAKER, M.D.

News and Comment

ANNOUNCEMENTS

Health Research Facilities Program.—On July 30, 1956, the President signed the Health Research Facilities Act of 1956, which authorizes the appropriation of funds not to exceed $30 million for each of three years to assist in the financing of the construction of facilities for research in the "sciences related to health." The Act defines "sciences related to health" as including medicine, osteopathy, dentistry, and public health, and fundamental and applied sciences when related thereto. The assistance is to be in the form of grants in aid to public and nonprofit institutions on a basis of not more than 50% for the Federal share. Items not creditable for matching purposes include (1) costs for the acquisition of land or off-site improvements and (2) obligations made prior to the award of the research facilities grant concerned. The Congress has now appropriated $30 million to the Public Health Service, Department of Health, Education and Welfare, for this program. These funds are now available and will remain available until expended.

The funds are to be used to provide additional research facilities through the construction and/or equipping of new buildings or the expansion, remodeling, alteration, and/or equipping of existing buildings.

The new law provides for the appointment of a National Advisory Council on Health Research Facilities. It is expected that this Council will meet in the near future to establish policies and approve regulations for the administration of the new program. The Surgeon General is not permitted to award a research facilities grant in aid which has not previously been approved by the Council.

Application forms, as well as additional information, will be supplied promptly upon request to the Division of Research Grants, National Institutes of Health, Public Health Service, Bethesda 14, Md.

Congress of Neurological Surgeons.—The sixth annual meeting of the Congress of Neurological Surgeons will be held at the Palmer House, Chicago, Nov. 1, 2, and 3, 1956. The secretary is Dr. Philip D. Gordy, 1007 Delaware Ave., Wilmington, Del. Dr. Wilder G. Penfield will be the guest speaker.

Congress of the American College of Surgeons.—The 42d Clinical Congress of the American College of Surgeons will be held in San Francisco, on Oct. 8 to 12, 1956.

The Neurological Surgery Advisory Council has arranged the program for the Clinical Congress, including two Surgical Forum sessions devoted to reports of research in the field of neurosurgery. On Friday, Oct. 12, there will be a panel discussion on "The Surgical Management of Intracranial Aneurysms and Arteriovenous Malformations," from 9 to 10:30 a.m., moderator, Russell Meyers, M.D., Iowa City, and a panel discussion on "Surgical Management of Cerebrovascular Disease Not Including Aneurysms and Arteriovenous Malformations," from 10:30 a.m. to 12:05 p.m., moderator, E. S. Gurdjian, M.D., Detroit. The discussions will take place in the Nob Hill Room of the Fairmont Hotel.

SOCIETY NEWS

New Officers of American Electroencephalographic Society.—At the Tenth Annual Meeting of the American Electroencephalographic Society, held in Atlantic City, June 15-17, 1956, the following were elected to office: President, Dr. John R. Knott, Psychopathic Hospital, Iowa City; President-Elect, Dr. Robert S. Dow, 1010 Medical Dental Bldg., Portland 5, Ore.; Secretary, Dr. J. K. Merlis, 150 S. Huntington Ave., Boston 30; Treasurer, Dr. Peter Kellaway, Baylor University, Houston, Texas.

Books

Clinical Recognition and Management of Disturbances of Body Fluids. By John H. Bland. Second Edition. Price, $11.50. Pp. 552, illustrated. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5, 1956.

The first edition of this work was titled "The Clinical Use of Fluid and Electrolyte." The present edition, though extensively rewritten, retains as its aim the presentation of deviations in fluid and electrolyte distribution in a form which will be useful at the bedside. After a very brief historical resumé, there are two chapters which present the basic physiological considerations in a lucid fashion. This is followed by a general clinical discussion and then by consideration of specific disease states in which fluid and electrolyte disturbances are prominent. Fluid disturbances in congestive failure, diabetes, renal disease, adrenal insufficiency, shock, and following surgery are presented, as well as a discussion of fluid metabolism in children, in the aged, and following exposure to heat. Three new chapters deal with fluid and electrolyte metabolism in diseases of the liver, in pulmonary disease, and in association with head injury. For each clinical state, consideration of normal mechanisms and their derangements is followed by a discussion of available therapeutic regimens and the dangers or complications with which these may be associated. Though dosages are often included, detailed regimens of therapy are wisely avoided. The book is written in simple language, with many diagrams to aid in visualizing the problems discussed. It is particularly well suited for the use of medical students and house staff but could be used with profit by physicians in their daily practice.

Multiple Sclerosis. By Douglas McAlpine, Nigen D. Compston, and Charles E. Lumsden. Price, 35 s. Pp. 304, with 115 illustrations. E. & S. Livingston, Ltd., 16 and 17 Teviot Pl., Edinburgh, 1955.

This volume was written by a neurologist in collaboration with a general practitioner and a pathologist. The three main objectives stated in the preface are "first to widen the general conception of the disease; secondly to provide an account of the early symptomatology and treatment; and thirdly to review the pathology and the relationship of multiple sclerosis to other dymyelinating diseases."

Each of these objectives is fulfilled. Various etiological factors are reviewed, as well as the theories of etiological mechanisms. A large section is devoted to the early symptomatology of the disease, emphasizing that it is the pattern of the behavior that renders multiple sclerosis unique. Clinical observations on the local spread of the disease are recorded and discussed. The cerebrospinal fluid is analyzed in respect to cells, protein, and colloidal reactions, along with the electrophoretic and immunochemical methods of quantitative analysis. The course of the disease is reviewed and the prognosis as to disablement and life expectancy is considered. Differential diagnosis is presented comprehensively, and treatment is outlined. The pathology of the disease and related demyelinating processs is illustrated by excellent plates of gross and microscopic changes. Throughout the entire volume there is frequent reference to various series of patients reported in the literature, as well as to the authors' own series of 1072 cases of multiple sclerosis, from 1930 to 1952. There are frequent brief case histories to illustrate a given fact.

This is a comprehensive, critical review of the problem of multiple sclerosis for the clinical neurologist or practitioner.

Section on PSYCHIATRY

The Human Body and the Human Being

(Special Article)

JAMES E. SHEA, M.D., New York

This paper is a review, by no means unprecedented, of some psychosomatic aspects of human behavior. Its scope comprises motivations and values, as well as reflex arcs and glandular secretions. For man is a physical body, capable of specifically human behavior—hate, tenderness, prejudice, hope, and despair. His ways are complex and contradictory; his actions puzzling and not easily predictable. What do we know, and what do we think we know, about the nature of man?

Traditionally, man has been regarded as a being composed of body and soul. In fact, the majority of Americans even today profess a belief in a soul which occupies the body and survives it after death. It is a matter of individual thinking how this concept of body and soul is perceived. Probably the body is regarded as a dwelling which the spirit (or soul or mind) inhabits. When the spirit acts—through its attributes of courage, faith, humility, or the rest—it uses the body to achieve its end. Thus, when the spirit is angered, the fist flies out. True, the spirit is somewhat affected by the limitations of the housing unit. Some poor souls are rendered feebleminded by defective masonry in the belfry. But it is further presumed that all dwellings are pretty much alike, built of standard bricks and straw. This notion about the interplay of body and soul, translated into more sophisticated terms, is the implicit philosophy of the "dynamic" school of psychiatric thought. To quote Ancel Keys[1]:

> Professional workers who deal with mental disease may be placed generally into two categories. The majority of practicing psychiatrists appear to regard the body as merely a vehicle or residence in which the mind pursues its own way to health or disease with relative independence from the state or history of the body. With the exception of gross trauma to the brain itself, they are inclined to recognize no physical factor as important in the etiology or in the treatment of the major psychoses and psychoneuroses. . . . On the other hand, there are the organicists, those experts who see or suspect, mostly the latter, an important physical aspect in mental disease—as cause or at least as a major influence.

The "organicists," then, do consider the body of the psychiatric patient. But it would be a mistake to think that they—the "organicists"—are themselves altogether lacking in crudity. Thus, Smith [2] was prompted to write:

> Our laboratory and clinical studies of alcoholics during the past several years have convinced us that alcoholism is a metabolic disease. Although alcoholism manifests itself primarily as a behavior problem, it occurred to us that perhaps the behavior disturbance was not the disease itself, but merely a symptom of an underlying metabolic process. There are many examples of behavior disorders arising from disturbed metabolic states. Hyperthyroidism, pernicious anemia, the menopausal state and cerebral arteriosclerosis frequently become apparent clinically because of the behavior disturbances they engender.

This is a good example of the conviction of many workers. It is difficult to make explicit these beliefs, since they are largely irrational and amorphous in the believer's mind. But the "organicist" does seem to

Received for publication June 2, 1956.

believe that mental disease (a concept he frequently does not stop to define) is caused by malfunctioning of the organs of the body. The belief is blurred in outline, even as conjecture: Perhaps the hypothalamus is the culprit. Or almost certainly the pituitary. And don't forget the genes. At any rate, shock treatment cures depressions, and lobotomy cures schizophrenia. Eventually some biochemist surely will find a cure for kleptomania, truancy, and marital incompatibility.

It should be clear that neither view—the "dynamic" or the "organic"—is of itself adequate to explain the phenomena of human behavior. One is at first tempted to scoff at a formulation such as Meduna's [3]:

> Human behavior can be understood in terms of the physiologic function of three sets of structures. The first set of structures is composed of afferent pathways conveying stimuli from within or without the organism of the brain. A stimulus arriving at the brain sets into motion a reverberating circuit between the cortex, thalamus and hypothalamus. The second set of structures utilizes positive and negative feed-back mechanisms. A positive feed-back mechanism is utilized when a stimulus arriving at these higher centers is experienced as pleasant. . . . If the arriving stimulus is experienced as unpleasant . . . a negative feed-back mechanism comes into play to obviate or minimize the impact of the stimulus. The circuits between cortex-as the stimuli, arriving through the afferent pathways, upset the homeostasis of the nervous system . . .
>
> Therefore, if we conceive of a psychoneurosis hypothalamus-thalamus-cortex reverberate as long as a failure of homeostasis, the psychoneurosis will depend upon the threshold of the structures participating in the reverberations between the cortex and lower structures of the brain. It is then predictable that every psychoneurotic condition, regardless of its symbolical content, can be treated by purely physical means. Thus, if the treatment can increase the threshold of stimulation of any part of the intrinsic feed-back mechanism of the brain, and suspend the reverberations within the system, the psychoneurosis will be modified or alleviated.

This sounds to the unfamiliar ear like the wilder outrages of science fiction, but, actually, it is not inconsistent with present-day hypotheses concerning the organization of the brain, as the work of Penfield and Kubie (to be quoted later) will show.

The reason it strikes us so harshly is not that most of us know so little about neuroanatomy and neurophysiology, but that it leaves out of account any recognizable human emotion. "A positive feed-back mechanism is utilized when a stimulus arriving at these higher centers is experienced as pleasant." Experienced as pleasant—there's the rub. Why are some stimuli experienced as pleasant? This is not really a problem for IBM, as Meduna seems to suggest. No one would quarrel with his formulation (though one might disagree with it) were it offered as the mechanism whereby emotions are implemented. But as a psychological theory it does rather drastically minimize the importance of the "symbolic content" of the psychoneurosis. There is ready acceptance of the view that the hypothalamus, as well as the adrenal gland, is involved in the hatred a man might feel for his neighbor, but why does he hate his neighbor? Is it because of reverberations in the cortex-hypothalamus-thalamus circuits? Or because the neighbor's radio is blasting the still of the dawn's early light?

The quarrel is not easily settled, even by the psychosomatic truce-maker. We speak still of "functional" psychoses as distinct from "organic" psychoses. We dichotomize phenomena into "mental" or "physical." Protest against this led Stanley Cobb [4] to the following declaration:

> I would like to make three assumptions which I believe can be upheld by scientific data in 1951.
>
> First: No biological process goes on without change of structure.
>
> Second: Whenever the brain functions, there is organic change.
>
> Third: The brain is the organ of the mind.
>
> If we accept these three, we must admit that "organic" change takes place whenever a person has a thought. This is an important function of the brain. All function is organic, so, the slang use of the terms "organic" or "functional" is meaningless. The same argument can be repeated substituting the terms "physical" and "mental."

This is undeniably true, but it is a truth which can lead to grotesque distortion in assessing human beings. This danger is illustrated by Walter Bruetsch,[5] who stated:

In answer to Dr. Cobb, who insists that we should forget about "either or," I may say that for some time I felt the same way. I changed my mind, and now I am quite emphatic that we should say "either or." This is particularly important in teaching because otherwise the student will never learn how to make accurate etiological diagnoses, which are so important for an intelligent treatment program. It is highly important, in my opinion, that a student learn to differentiate, for instance, between a depression as the initial symptom in a brain tumor or in general paresis, and a depression of psychogenic basis. Otherwise he will be a confused person the remainder of his professional life.

The issue is important, since it determines our treatment of patients. "Organic change takes place whenever a person has a thought." Conceded, though, to quote Bishop [6]:

It is difficult to conceive of a neural pattern corresponding to anxiety or to a dissociation from reality. If there is one, it must be too hopelessly complex to be recorded by any current apparatus.

We can even imagine, without too much strain, that pathological organic change takes place whenever a person has a delusional thought—for example, when the schizophrenic thinks he is Napoleon. But what of the deviationist in Russia who thinks Khrushchev is *not* Napoleon? What of his poor addled brain? Does the thought produce the organic change, or does the organic change produce the thought? (I do not mean in point of time, since obviously they occur concurrently; I mean in terms of etiological primacy—or what is known in logic as Efficient Causality.)

Gerard [7] says: "When experience leaves an enduring trace, it must be some sort of material imprint; and, so to speak, there can be no twisted thought without a twisted molecule." This is true in a way, but not necessarily in a neuropathological way. Error, or misconception, is not the same as disease. The cerebral molecular constellation of one who believes that Lincoln was the first president is different from the constellation of those who believe it was Washington. But if this is the result of poor instruction in history, how ought we to regard this twisted molecule?

This point is crucial, and one not to be dismissed by deploring the unscientific dichotomizing of mind and body. There are conditions, as Hoch [8] has demonstrated with mescaline, in which the organic change produces the thought. In the case of mescaline, these thought changes consist of delusions and hallucinations. There are other conditions in which the thought almost certainly produces the organic change.

The anxious, expectant father, pacing the hospital corridor, would be a classical example of the latter. It might be useful to look at the behavior of this expectant father, caught at this particular anxious moment. There is some evidence that people vary in their ability to withstand anxiety and deprivation. (This will be taken up again later, in a discussion of "physical" factors in neurosis.) We cannot wisely ignore the brain in which the reverberations are cycling, or the possibility that some brains are inferior circuits as circuits go. But we cannot ignore, either, the milieu in which the expectant father functions: his forgotten, but still active, sexual taboos; his rekindled competitive strife with father and siblings; his economic status. Perhaps one should even nod in passing to the Oedipus complex and castration anxieties.

The point is this: There is no valid reason why psychiatrists should subscribe to a "dynamic" versus an "organic" school of thought. However organically grounded they may be, abstractions such as guilt, self-contempt, and philosophical convictions are a necessary concern of the student of human behavior. The psychiatrist should conceive of them simultaneously as abstractions *and* neural patterns.

There is danger in any overemphasis on neurophysiology or neuropathology. It leads to a fatal oversimplification; to the belief that there will be no mental disease, and, one gathers, no human misery, if the neuropathology of people can be set right: Everyone will agree on the meaning of life and the proper living of life once metabolism is sufficiently understood. It is almost as

though such thinkers, in their haste to retreat from the thickets of metaphysics, become entrapped in what can only be called a sort of metachemistry.

It is likewise a dangerous oversimplification to ignore the physical substratum involved in the suffering of our patients. In many conditions—even perhaps in certain neuroses—the altered physical state is the main site of the problem. It is unreasonable to expect the tools of psychotherapy—transference, insight, reeducation, encouragement, dream interpretation—to be helpful in all behavior disorders not directly attributable to large holes in the head.

Our knowledge of human behavior is regrettably incomplete, even though the biochemists know a little, as do the psychodynamicists. We must work toward the day when the two disciplines will be correlated and we can justifiably speak of the biochemistry of psychodynamics.

Some questions which must be answered are these:

1. In a given disorder, for example, schizophrenia, is there evidence of a hereditary predisposition, when heredity is defined as "the transmission of potential physical and mental properties from parents to children through genes"?

2. Is there a known pathological state of the body accompanying the condition? Again, to take schizophrenia as an example, is there a metabolic alteration in the enzymatic range underlying the schizophrenic symptomatology?

3. Is the metabolic disorder the cause of the symtomatology or its result? For example, there is evidence that sugar metabolism is altered in patients hospitalized with a diagnosis of schizophrenia. Yet some workers are disposed to believe that this altered metabolism is the result of the schizophrenic's anxiety and not its cause.

4. Can we be sure that the changes found in certain conditions are specifically causative? Perhaps they are only tantalizing indices of some as yet unknown specific causes. For example, most observers will concede that a high preponderance of manic-depressives have a stocky build. (I use the phrase "stocky build" rather than some more technical term because I shall speak later on the technical difficulties involved in constitutional typology.) But stockiness is not the executive cause of the disorder, obviously. If it were, how could we account for the one-third of manic-depressives who are not stocky, or for the millions of stocky humans who do not develop manic-depressive psychosis?

5. How safe are we in arguing from analogy, or in presuming that facts true in one condition are applicable to another? For example, suppose that it is eventually proved that manic-depressive depression is caused by a disordered metabolism in the hypothalamus. What bearing does this have on normal grief? Is it merely an exaggeration of the bodily changes which accompany normal grief? Or are we misled by our own experiences with grief into thinking that the depression of the manic-depressive must be of the same nature? Perhaps the two are not really comparable, except in their grosser manifestations.

This paper will attempt to answer the above questions as they are applied to certain problems, namely, schizophrenia, alcoholism, homosexuality, and temperament, normal and abnormal. From a consideration of these, we shall learn something of the genetic, metabolic, and anthropometric factors in humans. The task is formidable, first, because of difficulties in methodology, and, secondly, because we are examining forms of behavior and not specific diseases. As Hoskins says[9]:

> It has yet to be proved that schizophrenia is an entity. It may be comparable to such diagnoses as "headache" or "hypertension," each of which has a common core manifestation but each of which may represent very dissimilar disorders.

Schizophrenia

Our knowledge of the genetics of schizophrenia stems largely from the work of Kallmann,[10] whose findings are compatible with those of other workers, such as Luxenburger, Rosanoff, Essen-Møller, and Slater.

It is Kallmann's contention that schizophrenia develops only in the carriers of a specific type of predisposition or potential vulnerability, and that this predisposition increases in proportion to the degree of blood relationship to a family member showing the psychosis. In other words, he uses the twin-study method to prove his contention.

The procedure is as follows: One studies the incidence of schizophrenia in the general population, step-sibs, half-sibs, full sibs, two-egg co-twins and one-egg co-twins. If the incidence is found to be overwhelmingly greater in one-egg co-twins than in the others, this is presumed to prove the presence of genetic, as opposed to purely environmental, influences.

Kallmann's findings are based on a study of 953 twin index families. The incidence of schizophrenia in the relatives of a schizophrenic patient are as follows:

Half-sibs	7.1%
Full sibs	14%
Two-egg co-twins	14%

Rather astonishingly, the incidence in one-egg twin partners is 86.2%. This seems convincing proof of the presence of a genetic factor as a strong causal component of schizophrenia. In this connection, Slater [11] says:

> Given that schizophrenia is a process which once set going is likely to produce irreversible change, we may easily account for its hereditary basis by a single mutant gene. It can be shown, however, that by itself this gene is not enough, and that other genetical and constitutional factors play a part, and the environment may itself either tend to protect the predisposed individual or to precipitate the psychosis. If the abnormal gene is a recessive one, the schizophrenic represents a homozygote and the schizoid personality may be a heterozygote. On the other hand, and this possibility would be available for either a dominant or recessive hypothesis, the schizoid personality might contain the entire specific genetical predisposition required to develop the disease, but be protected by subsidiary genes.

It is evident from this statement that our knowledge of how genetic factors operate is highly speculative. But our failure to understand the means whereby a result is obtained should not lead us to deny the result. We do not know how the antibiotics combat bacteria, but no one doubts their effectiveness in many diseases.

The work on the metabolic aspects of schizophrenia is so extensive that only the briefest outline is possible in this paper. A very full bibliography can be found in Altschule's recent book.[12] In trying to evaluate the significance of biochemical changes, it is wise to heed the warning of Hemphill and Rees,[13] who state:

> Great caution must be observed in interpreting abnormalities of total metabolism or of the endocrine system in mental illness, notably schizophrenia. They may be secondary to a primary disturbance of brain or to a central process responsible for the mental as well as the physical picture, or may themselves be the factor that determines the abnormal mentation.

Typical of the conflicting reports are the papers of Hoagland and his associates and Bliss and his associates. The Hoagland group [14] studied the response of the adrenal to stress in 200 normal subjects and 100 male schizophrenics who had been hospitalized for two and a half years. The patients and the normal control groups were subjected to a purely chemical stress (the ingestion of sugar by the Exton-Rose technique), to a psychomotor fatiguing test (the operation of a pursuit meter), and to a psychologic frustration test (target-ball test). The schizophrenic patients, in general, displayed abnormal and inadequate adrenal stress responses as compared with the controls. It is interesting that chronic schizophrenic patients, when not subjected to special stresses, give evidence of adrenal cortical secretion differing relatively little from that of normal controls. It is in response to stress that more marked group differences appear.

The chronic schizophrenic displays both quantitative and qualitative abnormalities of adrenal stress responses which appear to be specifically at the level of the inability of his adrenal cortex to respond to pituitary adrenocorticotropic hormone (ACTH) by release of normal amounts and normal ratios of steroid hormones.

On the other hand, the Bliss group[15] states:

Heretofore, all investigators have used as indicators of glandular activity such measurements as changes in the number of circulating lymphocytes and eosinophils; alteration in the concentrations of sugar, amio acids, and inorganic phosphate in the blood; variations in the urinary levels of potassium, sodium, uric acid, the creatinine-uric acid ratio, inorganic phosphates, 17-ketosteroids, and corticosteroids, or alterations in the sodium content of sweat.

Each of these elements, it is true, may be influenced by adrenocortical steroids, but with the exception of the urinary 17-ketosteroids and corticosteroids, all are nonspecific and often unreliable indicators of adrenocortical activity, since their concentrations are influenced by so many other physiological processes. Even in the case of the 17-ketosteroids, although they are metabolic products of steroids originating in the testes and adrenal cortex, Sayers[36] states:

"Urinary 17-ketosteroid output should be rejected as an index of adrenocortical activity . . . because of the lack of correlation between the rate of 17-ketosteroid excretion and adrenocortical activity as determined by other measures."

Consequently any conclusions about adrenal cortical activity based upon this evidence must be cautiously assessed with an awareness of the limitations of the techniques.

The findings of the Bliss group, using a technique of measuring adrenal steroids in the blood, are as follows:

Adrenocortical function of chronic schizophrenics was investigated. The concentration of adrenal steroids (17-hydroxycorticosteroids) in the peripheral blood was determined at 8 a.m.; after the intravenous administration of various amounts of ACTH or of a pyrogenic substance (Piromen); and after the subcutaneous injection of regular insulin. These drugs were employed to assess adrenocortical and pituitary-adrenocortical responsivity. Similar studies were made upon a comparable group of normal subjects. The adrenocortical and pituitary-adrenocortical reactivity of chronic schizophrenic and normal subjects were equivalent. There was no evidence of any impairment of adrenocortical physiology in the chronic schizophrenic patient.

Information concerning brain enzymatic changes is extremely scanty. To quote from Pope[17]:

Most of the published material on enzymes in psychiatric conditions has been reports of studies on blood or cerebral spinal fluid and these unfortunately afford little insight into the state of affairs in the cerebral tissue itself. . . . The study of enzymes in the brains of those with mental illness has been limited to a few pioneer investigations. . . . Only with the advent of the various forms of psychosurgery has it become possible to obtain brain tissue in the form of biopsies under relatively standardized and biochemically sound conditions. The pioneer quantitative work on brain enzymes in the mentally ill has been that of Dr. Winifred Ashby upon carbonic anhydrase. The exact role of this enzyme in the nervous system is unknown, but her work has indicated that embryologically its appearance coincides with the onset of function, and it is to be supposed that it has an important role in the hydration and dehydration of carbon dioxide and hence in the maintenance of tissue acid-base balance. . . . Dr. Ashby has reported abnormalities in its distribution in the brains of schizophrenics, with decreases in some cortical areas relative to the rest. She feels that this might be of significance in relation to hypothetic changes in relative rates of discharge of the neurons in the affected areas.

Pope summarizes a report of his own work on biopsy specimens of two groups of lobotomized patients. The first group was composed of nonpsychotics lobotomized for intractable pain or psychoneurosis. The second was composed of profoundly psychotic patients having a diagnosis of schizophrenia. He states:

When the cholinesterase activity of each biopsy specimen as a whole was computed and compared with the clinical diagnosis in the case of those twelve patients most rigidly fulfilling the clinical criteria described, it was found that five of seven patients among the deteriorated schizophrenics exhibited an overall cortical cholinesterase activity in excess of the range of activities found among the relatively normal pain-psychoneurosis patients. Obviously, these are far too few observations to be more than suggestive, and even though this trend were fully established, its meaning is obscure. All that can be directly inferred is that the prefrontal cortex of some of the deeply psychotic patients hydrolyzed acetylcholine faster than usual. If cholinesterase activity is an index of the rate of turnover of the system metabolizing acetylcholine, and if the latter is a compound of critical importance in the physical chemistry of impulse initiation, propagation, and synaptic transfer, it might suggest a chronic increase in rate of neuronal discharge in the cortex in question. Such an hypothesis would not be entirely out of line with certain other reported findings.[17]

What is to be made of all this? Is it a likelihood that the person who succumbs to schizophrenia is normal as regards his bodily

equipment, and that the psychosis is the result only of early and grievous deprivations of love and maternal support? Perhaps. But another hypothesis must be entertained. It has been stated by Hoskins[9] as follows:

> I would propose that the schizophrenic psychosis represents an end result of a generalized failure of adaptation that arises from defective evolution of the maturing processes. It is possible that the postulated immaturity might have its fundamental origin in a specific pathology—e. g., abnormalities of one or more enzyme systems in the brain. . . . The psychosis might be regarded as a functional disintegration of the personality due to an inability to meet the demands of maturity with the resources of the immature.

Alcoholism

Let us turn now to a consideration of the work on the "organic" aspects of alcoholism.

Most of the publications in this field come from Smith, Lovell and Tintera, and Williams. No real work on the genetics of alcoholism has been published up to the present.

There has, likewise, been no attempt to evaluate cases from the anthropometric point of view. Smith[2] speaks of abnormal hair distribution of the alcoholic, and Tintera and Lovell[18] refer to the "younger asthenic males whom we have come to regard as highly potential alcoholics." Such statements are not convincing as serious attempts to correlate data within the framework of any of the usual present-day systems of constitutional typology.

Concerning metabolism, however, the situation is different. Here, a great deal of work has been done, much of it of questionable scientific value. The claim has been made that alcoholism is a metabolic disease. The alcoholic is thought to suffer from an adrenal insufficiency, possibly secondary to a pituitary deficiency.

This claim is very difficult to prove. As Bliss has pointed out, the various tests used to measure adrenal function—blood sugar curve, eosinophil count, 17-ketosteroid elimination, and so on—are not specifically indicative of adrenal function. In severe cases of hypoadrenalism the interpretation of these tests is easy enough. But in marginal—not to say hypothetical—states of deficiency the meaning of a flat blood sugar curve, for example, is questionable. It can indicate anything from liver disease to insufficient food intake in the previous few days.

Concerning blood sugar, Lovell and Tintera[19] state:

> In the study of alcoholic patients, hypoglycemia was found universally during their "dry" periods. The average fasting blood sugar level was 60.9 mg. per 100 cc., the range varying from 54 mg. to 80 mg. per 100 cc.

There is no mention of the number of patients studied or of the period of sustained sobriety at which the study was made. It is doubtful whether a single fasting blood sugar determination is much of a test of adrenal function. Moreover, the effect of emotion on blood sugar has been extensively and carefully investigated by Portis and Alexander,[20] among others, who found marked fluctuations in blood sugar levels in many people, most of whom were not alcoholics at all.

Likewise, Lovell and Tintera[18] state:

> In addition to their effect upon the utilization of carbohydrate, the adrenal cortical steroids play a role in regulatory androgen function. Many alcoholic patients reveal deficiencies in this regard as determined by urinary 17- ketosteroid determination.

Again, no mention is made in this paper of the number of alcoholic patients studied, or of other tests of adrenal function, or of why the authors did not utilize the techniques of adrenal stress response which Hoagland found useful in the study of schizophrenics. True, in another paper,[21] these authors do state, "Our patients, now numbering over 1000 on whom 17-ketosteroid determinations were made, revealed almost universal deficiencies in this regard." The exact 17-ketosteroid excretion figures are not mentioned.

As a matter of fact, it is often hard to interpret the significance of 17-ketosteroid excretion rates. Lovell and Tintera's control group, for example, showed the same

low 17-ketosteroid excretion figures as did their patients, and for this reason were considered to be potential alcoholics.

Voegtlin's [22] investigations do not confirm the helpfulness of hormonal therapy reported by Lovell and Tintera. Since the particular hormone preparation used by these authors is one of very slight, almost nonexistent, strength, this is not hard to understand. In a study of 39 alcoholic patients treated with prolonged courses of cortisone and lipoadrenal extract, he found that "less than 20% of the patients observed for a period of one year remained abstinent."

There appears to be considerable evidence that adrenal dysfunction is common enough in alcoholism, *secondary* to the alcoholism, as shown by Lester and Greenberg [23] and others. But until carefully controlled work is done (preferably using the measurement of concentration of adrenal steroids in peripheral blood), the question of a primary predisposing metabolic disorder in the alcoholic must be considered unanswered.

Williams [24] has advanced the genetotrophic theory of the etiology of alcoholism. A critique of this theory was published by Popham,[25] and what follows is largely a restatement of his views. Briefly, this theory is to the effect that certain persons possess distinctive, inherited metabolic patterns which predispose them to alcoholism. Alcoholism is said to be a genetotrophic disease because it is thought to arise fundamentally from nutritional deficiencies which, in turn, are genetically controlled.

The alcoholic is regarded as a person who possesses, because of genetic blocks, a biochemical spectrum featuring a relatively heightened need for vitamins or other elements of nutrition, not supplied by the diet. There is diminished production of one or more specific enzymes. The relative nutritional deficiency of such persons leading to an inability to utilize essential foodstuffs in the diet is thought to cause a craving for alcohol.

The rational therapy for such persons is simple: the feeding of vitamins, for example, in amounts necessary to satisfy the deficiency.

The background from which this theory springs is intricate and compounded of elements such as genetics and biochemistry, with which the average doctor is not familiar. For example, what is meant by "distinctive metabolic patterns"? It is not a concept generally accepted biochemically, and certainly there is no real evidence for metabolic individuality in relation to alcohol.

Even the laboratory procedures used by Williams must be considered somewhat suspect. Thus, he establishes the fact that rats fed a vitamin-deficient diet will choose to drink an aqueous solution of alcohol when offered a choice between such a solution and water, and that the amount of alcohol drunk will be significantly decreased if certain substances, vitamins or others, are added to the deficient diet.

But what does this mean? A choice between an alcohol solution and water may be no choice at all if the animal requires calories of a type which are available to it only from the alcohol. The reason that rats choose an alcohol solution in preference to ordinary water has not been comprehended: Is it a matter of taste, of calories, or a need for a central nervous system depressant? Is it because sufficient carbohydrate or fat or protein is lacking in the diet?

Lester and Greenberg [26] conducted experiments in which they offered their rats a third choice, with interesting results. The third choice offered was, in one instance, a sucrose solution; in another, a saccharine solution, and, in the final instance, a solution of fat with solid sucrose added. All of these resulted in decreased alcoholic intake, with sucrose leading the list. Lester and Greenberg concluded that the effects of the sucrose may be due to its palatability, its caloric content, and its form, or to still other causes, since fat, solid sucrose, and saccharin all reduced the intake of alcohol but not to the same extent as the solution of sucrose. In

fact, a solution of sucrose almost abolished the intake of alcohol. These findings demonstrated that there is no preference for alcohol specifically.

It must be emphasized that Williams' work was, with one exception, conducted on rats and that rats do not drink for the same reasons as do humans. Attempts to confirm Williams' theories in humans are few and in general do not bear out his contentions. Thus, Smith, Dardin, and Brown [27] gave pantothenic acid and other components of the vitamin B complex to chronic alcoholics, with unimpressive benefit.

Homosexuality

In an examination of the genetic and so-called "organic" aspects of homosexuality, again, we are greatly indebted to Kallmann.[10] He examined a consecutive series of 95 predominantly or exclusively homosexual twin index cases of the male sex. In the two-egg group, nearly 60% of the co-twins of distinctly homosexual subjects show no evidence of homosexuality at any age, and only 11.5% of this group of co-twins have been given homosexuality ratings of 5 or 6 on Kinsey's schema.

In contrast to this, overt homosexuality was found to be present in 44 out of 45 one-egg twins. These twins, moreover, tended overwhelmingly to be similar in the role they take in their individual sex activities, as well as in the extent of feminized appearance and behavior displayed by them.

To forestall objections that perhaps the twins inducted each other into homosexual practices, Kallmann found that, in general, the concordant twin partners claim that they developed their sexual tendencies independently and often apart from each other. All of them categorically deny any mutuality in overt sex relations.

Many will concur with Kallmann in the statement [10]:

> These twin data throw considerable doubt on the validity of purely psychodynamic theories of certain types of homosexual behavior patterns in adulthood, while strengthening the hypothesis of a gene controlled disarrangement in the balance between male and female maturation (hormonal) tendencies. The adaptational equilibrium between the potentialities of organic sex differentiation and the consequent pattern of psychosexual behavior are apparently so labile that the attainment of a maturational balance may be disarranged at different developmental stages and by a variety of disturbing mechanisms. In any case, the intersexuality theory, or, more precisely, a genetically oriented "imbalance" theory—although still based on statistically insufficient and cytologically unconfirmed evidence—can no longer be regarded as an implausible explanation for certain groups of male homosexuals.

The intersexuality theory may need further discussion. It was developed by Lang,[28] who, in turn, used the theory of sex intergrades of Goldschmidt. Male-sex intergrades are organisms which morphologically show all typical male characteristics, although their cells are genotypically determined by a female set of chromosomes.

Goldschmidt did his work on the gynandromorph, an insect with male and female characteristics mosaically distributed throughout its body. He found that he could experimentally establish successive stages of intersexuality from the full male through slightly and markedly feminized males to the completely transformed female-sex intergrade. He also experimentally produced a set of intersexes ranging from complete female through all intermediate stages to the male-sex intergrade.

From this starting point, Lang argued as follows: If it is true that a percentage of male homosexuals are real male-sex intergrades who are genetically female but who have lost all female morphological sex characteristics except their chromosome formula, then an undue preponderance of males should be found among the siblings of male homosexuals. If hereditary factors were operating in accord with the discussed genetic theories of intersexes, the effect would be more pronounced in persons with more complete renunciation of heterosexual activity.

Lang studied 1015 cases of homosexuality taken from the police files in Germany. He found a male-female ratio of 121:100 rather than the normal 106:100. In the group aged

over 25, which would consist of the more confirmed homosexuals, the ratio was 128.3 : 100.

Obviously, this theory is open to certain doubts from the statistical point of view, even assuming that one can translate into terms of humans what is true of gynandromorphs. As a theory, it is ingenious but unverified. Similarly unsatisfactory are most other investigations of the "organic" factors in homosexuality.

Anyone who wishes to survey the available knowledge in their field is referred to the work of Beach,[29] who says in part:

> An exaggerated notion of the specificity of hormonal effects upon mating behavior in lower animals together with lack of appreciation of the relative importance of sociopsychologic versus physiologic influences in man, has led some investigators to conclude that sexual aberrations in the human may be referred in rather simple fashion to endocrine abnormalities. . . .
>
> It has been widely accepted that gonadal hormones are behaviorally sex-specific; this is to say that ovarian hormones normally facilitate feminine mating responses, while testicular hormones are ordinarily associated with the masculine sexual pattern. In one sense this is true, but the form of behavior which is elicited by endocrine manipulation is a joint product of the chemical constitution of the hormones and the genetic constitution of the organism under observation. . . . It cannot safely be concluded that masculine sexual performance is always inhibited by estrogen and may be stimulated only by androgen. Goodale [30] states that a sexually inactive capon which was implanted with ovarian tissue later began to crow and tread hens.

Therefore, male and female behavior is not to be conceived of simply in terms of male and female sex hormones. In this respect, the work of Ellis [31] is pertinent. He surveyed the reports of sexual behavior and libido of 84 human hermaphrodites and found that in the great majority of cases the preferred sex role and direction of desire corresponded to the masculine or feminine upbringing, regardless of the nature of the external and internal sexual morphology. He concluded that the determination of psychogenic sexuality in these cases depended primarily upon environmental factors and was relatively independent of possible hormonal effects.

Typology

Let us turn now to the intricacies of constitutional typology. This particular subject has a long history. It dates back at least to the time of Hippocrates, who distinguished a *habitus apoplecticus* (short and fat) from a *habitus phthisicus* (long and thin).

Different anthropometric classifications have prevailed at different times. At present the best-known systems are those of Kretschmer,[32] Rees and Eysenck,[33] and Sheldon.[34] Since Sheldon's system is the most influential in this country, it will be discussed in greater detail.

Sheldon says:

> [A] somatotype is a series of three numerals, each expressing the approximate strength of one of the primary components in a physique. The first numeral always refers to endomorphy, the second to mesomorphy, and the third to ectomorphy. When a 7-point scale is used, the somatotype 7-1-1 is the most extreme endomorph, the 1-7-1 is the most extreme mesomorph, and the 1-1-7 is the most extreme ectomorph.
>
> Endomorphy, or the first component [refers to] relation predominance in the bodily economy of structure associated with digestion and assimilation. [It implies] relatively great development of the digestive viscera.
>
> Mesomorphy, or the second component [refers to] relative predominance of the mesodermally derived tissues, which are chiefly bone, muscle and connective tissue.
>
> Ectomorphy, or the third component [refers to] relative predominance of the skin and its appendages, which include the nervous system.

In addition to these, Sheldon measures such various components as the following:

(*a*) "Dysplasia," calculated from five bodily regions.

(*b*) "Gynandromorphy. The g component. The degree of predominance of feminine characteristics in a male physique, or of masculine characteristics in a female physique." He calculates also primary and secondary *g*—primary referring to those gynandroid characteristics which are readily manifest in the standard somatotype photo-

graph, and secondary referring to the gynandroid characteristics picked up on closer inspection, especially at physical examination.

(*c*) "The t component. The component of thoroughbredness. A rating on the aesthetic quality of the physical structure. . . . The t component is really aesthetic pleasingness." This component is also divided into primary and secondary.

(*d*) "Aesthenia." This is not to be confused with Kretschmer's aesthenic *type* of physique. As Sheldon uses the word, it refers not to the somatotype but "to the condition of being abnormally weak for the somatotype."

(*e*) "Gnarled mesomorphy." This refers to bodies which are "strong, often extremely strong, but are usually heavy and cumbersome, with massive torsos and short legs. They are built close to the ground and suggest stunted, gnarled trees growing near the timberline."

(*f*) "Aplastic mesomorphy." This refers to mesomorphs who have not "filled out" to a normal mesomorphic degree. "These youngsters somehow suggest leaves which, touched by frost, never unfolded properly yet have retained sufficient or even high vitality."

There can be no doubt that Sheldon has a system. How good a system it is, however, is quite another matter. In the first place, it is not as objective as the uninformed might think. In fact, Sheldon explicitly defends his right to subjective evaluations. In "Varieties of Human Temperament,"[35] he compares the task of the constitutional psychiatrist to that of a leather sorter or a wine taster. In "Varieties of Delinquent Youth,"[34] he says:

> It is not quite a foolproof measure. For judgments of t [by *t* he means, as above, the component of thoroughbredness] to have validity, the judges must have both aesthetic intelligence and integrity. They must be able to recognize beauty of proportion even though they may have racial and somatotype preferences or prejudices of their own. Achievement of such aesthetic integrity is not as difficult as might be feared. I have found that the average graduate student, when first undertaking a series of ratings of primary t from a radically mixed series of somatotype photographs, achieves a correlation of about +.80 with my ratings. For a few the correlation is almost perfect at the outset. For a few it is as low as +.50.

The issue is clear. Validity is established when the student's aesthetic judgments conform to Sheldon's. And Sheldon—one must presume—knows what's beautiful.

Sheldon's statistics have not escaped criticism. Adcock[36] undertook a study of Sheldon's figures but, in spite of several attempts, discovered that he was faced each time with the problem of finding the root of a negative number. He remarks, "Obviously there is something peculiar about these intercorrelations." Lubin[37] says about the intercorrelations that "the peculiarity is so great that one is forced to ask whether it may not be outside the bounds of mathematical probability."

In considering typology, what particular measurements ought to be made? Evidently not just those of Sheldon's. Other "constitutionalists," such as Eysenck, criticize Sheldon for not giving sufficient importance to the factor of body size. The latter says,[38] "The general body size may be of greater importance for personality than body type."

Even working within the framework of Sheldon's system, there is the possibility that the somatotype may not remain constant, despite his assertion that it does. This, at any rate, was the conclusion of Lasker,[39] an anthropologist, who placed 34 volunteers on an insufficient diet for 24 weeks. During this period the subjects lost an average of 24% of their body weight. Photographs were taken at the beginning and at the end of this period, and the somatotyping technique was applied. Lasker found that every subject showed a significant change in somatotype, all the measurements tending to decrease.

Eysenck * says, concerning Sheldon's work:

> The figures given by him are interesting, but like so much else in his work, they are given *en passant*, without very much information being

* Eysenck,[38] p. 70.

vouchsafed regarding conditions of the experiment, the controls adopted, or any of the other attendant circumstances which must be known before a judgment can be made.

The difficulties of body typology are trifling, however, when compared with attempts to deal with types of personality or temperament. Thus, Kretschmer,[32] with some approximate justice, can divide people into pyknic, asthenic, athletic, and dysplastic body types. But when it comes to temperament, he speaks, for example, of the "sensitive, cold, aristocratic type" and of "the type of pathetic idealist."

Sheldon[35] speaks of "viscerotonia, the first component of temperament . . . endomorphy is the same component measured at a purely structural or morphological level." Viscerotonia comprises 20 traits, among which are listed "love of physical comfort, tolerance, need of people when troubled, love of polite ceremony."

"Somatonia" is the second component of temperament measured at the least-conditioned level of dynamic expression. Mesomorphy is the same component measured at the morphological level. Sheldon lists 20 traits which can be used to measure this component. They include "the energetic characteristic," "psychological callousness," "the unrestrained voice," and "claustrophobia."

"Cerebrotonia" is the component of temperament which corresponds with ectomorphy, and its 20 traits include "love of privacy," "agrophobia," "need of solitude when troubled," and "vertical mental cleavage, introversion."

Factor analysis is a discipline at least as difficult as psychoanalysis and as controversial. But, to evaluate typology, some understanding of it is needed. A competent working knowledge of this subject can be gained from a study of Eysenck's "Dimensions of Personality."[38] Despite methodological controversy, many serious workers find factor-analytical confirmation of the theory that the shape of the body and the personality are related in some fashion as yet largely unknown.

For example, Rees[40] conducted an anthropometric investigation of 200 soldiers suffering from effort syndrome. The group as a whole was found to be significantly more leptomorphic than a comparable control group. The term leptomorphic corresponds to Kretschmer's asthenic or Sheldon's ectomorphic group.

Rees and Eysenck,[33] using their own system of typology, which examined 18 body measurements, and of personality typology, which included 200 psychiatric trait ratings, conducted an investigation on 400 neurotic British soldiers and 100 non-neurotic soldiers. Their findings follow:

1. "The leptomorphs tend to show a higher proportion of schizoid personality traits than do the eurymorphs." (The eurymorph group is the same as the pyknic or endomorphic.)

2. "The neurotic group contains a significantly higher number of leptomorphs and eurymorphs and a significantly smaller number of mesomorphs than does the normal group."

Seltzer[41] conducted an investigation of 258 normal Harvard undergraduates. His findings are summarized thus:

> Individuals possessing disproportions have a greater frequency of personality traits indicating lesser stability, lesser integration, greater sensitivity and complexity of the personality and lesser capacity for making easy social adjustments.
>
> Conversely, individuals with traits indicating "soundness," stability, integration, vitality and strength of personality have fewer disproportions in their physiques than the average of the group.

Similar were the impressions of Cabot,[42] who found in 212 normal boys "a most striking superiority of the athletosomes . . . in regard to such traits or patterns as competitiveness, influence, ascendence, social leadership." He postulates a theory that "constitutional advantage of 'good' physique is a strong determinant of traits fundamentally social in genesis and development."

But, as usual, there is dissension.

Fiske[43] conducted his studies on 133 boys, aged 13 to 17, who were students at a private school. He found that on intelligence testing there was no significant relationship

to somatotype group. Regarding personality tests, he found that "the number of significant findings in this study of adolescent boys is not greater than chance expectancy. The use of Sheldon's improved procedure for classifying physique yielded the same paucity of significant relationships to physique that has been found in earlier studies."

Kleinberg and his associates [44] conducted their investigation on two groups of students: the first, Columbia undergraduates; the second, Barnard undergraduates. Concerning their results on the male subjects, the conclusions are these:

> From a group of 153 subjects, homogeneous in age, sex, education, social and economic backgrounds, two sub-groups, leptose and pyknic, were selected on the basis of physical criteria. A number of mental tests were administered to both groups and their performances were compared. No reliable differences were found between the physical groups on any mental tests.

The most surprising dissident voice of all is Sheldon's. In "Varieties of Temperament," [35] he says:

> If anything is demonstrated conclusively by the study as a whole, it is this: that neither the somatotype alone, nor any other single factor, will suffice to "explain" a personality. Persons of the same somatotype frequently develop into singularly different kinds of people. . . . So many (apparently secondary) variables are at work that the *specific manifestations* of temperament can be predicted from the somatotype only within very wide limits.

How wide these limits are can be shown by quoting his conclusions in Chapter 7:

> Among the two hundred cases, perfect agreement between somatotype and temperament occurs in 14 cases. Eleven cases show "radical disagreement" [his phrase] between temperament and somatotype.

Temperament and morphology are not to be easily correlated, then, any more than are sexual disposition and endocrinology. Equally difficult is any attempt to correlate morphology and heredity, and heredity and temperament. On this score, Cattell [45] says:

> Evidence [of the role of heredity in personality] is regrettably fragmentary and so uneven in reliability that it is very difficult as yet to construct any scientifically satisfactory over-all picture.

Hall [46] says:

> In order to have a science of psychogenetics it is not sufficient to determine merely that certain behavior traits are genetically transmitted. This is the first step. Genetic analysis, the mapping of chromosomes and the specification of the *modus operandi* of the genes are also necessary functions of the psychogeneticist.

Conclusions

I have sought in this paper to examine some of the evidence concerning the "physical" factors involved in human nature and human behavior. As a result of this study, I have arrived at certain conclusions.

1. There is incontrovertible evidence that certain modes of behavior are genetically determined. Among these are certain cases of homosexuality and schizophrenia. The evidence is equally strong in manic-depressive psychosis and other conditions, which for reasons of space are not discussed in this paper.

2. It is likely that genetic factors are involved in criminality and psychoneurosis. Temperament, also, probably has its genetic aspects. That is to say, genes may well have something to say about whether we are delinquent or law-abiding, happy or gloomy, radical or conservative.

3. The importance of the genetic element varies enormously in different conditions. It plays a more important role in Huntington's chorea, for example, than in juvenile delinquency. Environmental factors, in the case of the latter, provoke the predisposed, or the somewhat predisposed, in a fashion that is not true of specific neurological disorders. The topics under discussion in this paper—schizophrenia, alcoholism, homosexuality, temperament—were chosen to illustrate precisely this point, and were not the result of a Wagnerian obliquity on my part.

4. The ways in which the genes operate to produce their result is almost completely unknown. There are virtually no hypotheses, good, bad, or indifferent. Listen to what the geneticists have to say:

Haldane [47] says: "Each gene is responsible not for a unit character such as form or color, but for a unit biochemical process. Its status in the cell may be compared with that of an organ in the whole body."

Catcheside [48] says: "A gene is primarily a hypothetical entity postulated to explain the results of breeding experiments."

Penrose [49] says:

According to present-day standards in human genetics, it is insufficient to classify diseases as recessive, dominant or sex-linked. . . . With imperfectly recessive conditions (usually called dominant) i. e., those which are manifested in the heterozygote, variations of severity as between individuals and at different times in the same affected subject are the rule. Sometimes the condition amounts only to a susceptability to a disease or a diathesis.

And, finally, Kallmann [10] says:

No adequate estimate can as yet be made as to the total number of genes in a human chromosome. . . . While chromosomes are visible microscopically and can be analyzed chemically as consisting largely of nucleo-proteins . . . it is not yet possible to see or to analyze directly a gene unit. What is known about the chemical structure of genes is based on evidence obtained either by the ultraviolet action spectrum of gene mutation, or by comparison with viruses. Genes are believed to be minute protein particles with high degree of specificity and the stability of their specific properties apparently rests on certain protein or nucleic components, or both."

5. It may be that certain behavior disorders are the result of biochemical changes, either in the brain or in the body as a whole. But the evidence is as yet inconclusive and fragmentary. The experts in biochemistry, such as Pope, are most modest in their claims. This is not to say, however, that biochemical changes are unlikely etiological agents. We must conclude only that at present we just do not know.

6. There is evidence that morphology and behavior are somehow related. For example (and it is almost the only valid example), there is a genuine difference in body build between groups of schizophrenics and groups of patients with manic-depressive psychoses. But how much farther in this direction can we go at present? It is impossible to explain behavior, as Sheldon † tries, with this formulation:

This is a viscerotonic-nice personality but cerebrotonia appears to be at least normally represented. He lacks aggression and lacks sonototonic energy in general. . . . The temperamental pattern is probably normal to this sonototype, with an endomorphic control room matched against an ectomorphic boiler and driving machinery.

What is "cerebrotonia," after all? Only a word, not a thing, in the sense that ACTH and adrenaline are things. Even as a word, or a concept, it hardly represents an advance over "libido" or *élan vitale*. Here, again, we must be content with a moderate conclusion, namely, that physique does determine temperament in some fashion too complicated for us to understand with our present knowledge.

7. It is obvious that psychiatry in the future will profit from more extensive and precise knowledge of the biochemistry of thought and emotion. But even lacking this knowledge, there is something we can do. We should try, in our thinking, to encompass both the "dynamic" and the "physical" point of view. We should try to think of the frightened, anxious patient in terms of his stress-ridden adrenal glands and metabolite-laden cortical cells. But we should give due regard, also, to the content of the fear, in all its furtive complexities. Such a dualistic approach can have important therapeutic consequences. To quote Kubie [50]:

There may be a neurophysiological mechanism for both normal and pathological repetitive phenomena, and this mechanism may consist in part of reverberating circuits along which nervous impulses not only can re-excite themselves, but in so doing may also isolate themselves in varying degrees from external influences. For example, such an isolation could conceivably occur whenever the time relationships in the circuit are such that when the excitatory process has subsided, the whole circuit goes into a refractory state. Under such circumstances there would seem to be no way in which action currents from elsewhere in the nervous system could exert an influence upon the closed circuit. This would constitute an organic limitation on any form of psychotherapy.

Here we must remind ourselves that however plausible the hypothesis, the existence of such circuits remains a hypothesis. Yet the mere hypothesis opens up various alternatives to current conceptions both of the pathogenesis and of the maintenance of the neurotic process. For instance, structural or biochemical variations in the central nervous system might render one nervous system more liable than others to the formation of self-exciting circuits. Precise investigations of such

† Sheldon,[51] p. 621.

constitutional variants as these wait upon the development of refined electrophysiological and microchemical techniques. Such a closed circuit might offer a possible physiological explanation of the well-known clinical fact that once such repetitive disturbances are established, whether as a result of organic or of psychological causes, they may prove resistant to psychological influences.

In affective disturbances, where this is particularly true, the circuitous courses of the reverberating waves with their autonomic involvement are of special interest, and in this connection it is relevant to note that such isolating circuits could explain the efficacy of shock therapies which by interrupting reverberating circuits could render the individual accessible both to external psychological influences and to his own inner controls.

From the viewpoint of therapy, then, it might at times be irrelevant to determine whether the disorder is the result of heredity or environmental factors. A fear, or an attitude, or a trait, however it arose, may be locked in the cells of the patient's body, stone deaf or inaccessible to psychoanalytic blandishments and pleas. Every psychotherapist must have encountered many such patients. It should follow that the "dynamicist" need not banish from his thoughts the idea of electroshock or psychosurgery, the gas mask, or the hypodermic needle. In reciprocation, perhaps the "organicist" will forego the temptation to think of all human unhappiness as the by-product of a high blood pressure, or a low blood sugar.

For truth is very elusive, and the whole truth about anything lies quite beyond human grasp. We must never forget that there is dust in the air and a mote in the eye. In psychiatry, all our present-day techniques for influencing human behavior are not so brilliantly effective that we dare become complacent. This is as true of histamine therapy, carbon-dioxide therapy, and shock therapy as it is of psychoanalysis in its original form or its various heretical derivatives.

It is my suggestion that our knowledge will grow if we renounce our sectarian biases and listen to what our neighbor in the next camp, or discipline, has to say.

REFERENCES

1. Keys, A., in The Biology of Mental Health and Disease, Milbank Memorial Fund, New York, Paul B. Hoeber, Inc. (Medical Department of Harper & Brothers), 1952, p. 515.

2. Smith, J. J.: A Medical Approach to Problem Drinking: Preliminary Report, Quart. J. Stud. Alcohol 10:251-257, 1949.

3. Meduna, L. J.: A Neurophysiological Theory of Psychoneuroses, J. Nerv. & Ment. Dis. 110:438, 1949.

4. Cobb, S., in The Biology of Mental Health and Disease, Milbank Memorial Fund, New York, Paul B. Hoeber, Inc. (Medical Department of Harper & Brothers), 1952.

5. Bruetsch, W., in The Biology of Mental Health and Disease, New York, Paul B. Hoeber, Inc. (Medical Department of Harper & Brothers), 1952, p. 326.

6. Bishop, G. H., in The Biology of Mental Health and Disease, New York, Paul B. Hoeber, Inc. (Medical Department of Harper & Brothers), 1952, p. 161.

7. Gerard, R. W.: The Biological Roots of Psychiatry, Am. J. Psychiat. 112:81-90, 1955.

8. Hoch, P. H.: Experimentally Produced Psychoses, Am. J. Psychiat. 107:607, 1951.

9. Hoskins, R. G.: The Biology of Schizophrenia, New York, W. W. Norton & Company, Inc., 1946.

10. Kallmann, F. J.: Heredity in Health and Mental Disorder, New York, W. W. Norton & Company, Inc., 1953.

11. Slater, E.: The General Aspects of Personality and Neurosis, Tr. International Congress of Psychiatry, Paris, Hermann & Cie, 1950, vol. VI, pp. 133-134.

12. Altschule, M. D.: Bodily Physiology in Mental and Emotional Disorders, New York, Grune & Stratton, Inc., 1953.

13. Hemphill, R., and Rees, W. L., in Perspectives in Neuropsychiatry, edited by Derek Richter, London, H. K. Lewis & Co., Ltd., 1950.

14. Hoagland, H., in The Biology of Mental Health and Disease, Milbank Memorial Fund, New York, Paul B. Hoeber, Inc. (Medical Department of Harper & Brothers), 1952, pp. 434-447.

15. Bliss, E. L.; Migeon, C. J.; Hardin Branch, C. H., and Samuels, L. T.: Adrenocortical Function in Schizophrenia, Am. J. Psychiat. 112:358-365, 1955.

16. Sayers, G.: Adrenal Cortex and Homeostasis, Physiol. Rev. 30:241-320, 1950.

17. Pope, A., in The Biology of Mental Health and Disease, Milbank Memorial Fund, New York, Paul B. Hoeber, Inc. (Medical Department of Harper & Brothers), 1952, pp. 457-466.

18. Lovell, H. W., and Tintera, J. W.: Alcoholism: Recent Advances in Its Treatment, M. Times 80:191-198, 1952.

19. Lovell, H. W., and Tintera, J. W.: Endocrine Treatment of Alcoholism, Geriatrics 4:274-280, 1949.

20. Portis, S. A., and Alexander, F.: A Psychosomatic Study of Hypoglycemic Fatigue, Psychosom. Med. 64:41-60, 1944.

21. Lovell, H. W., and Tintera, J. W.: Hypoadrenocorticism in Alcoholism and Drug Addiction, Geriatrics 6:1-11, 1951.

22. Voegtlin, W. L.: Treatment of Alcoholism with Adrenal Steroids and ACTH, Quart. J. Stud. Alcohol 14:28-37, 1953.

23. Lester, D., and Greenberg, L. A.: Alcoholism, 1941-1951: A Survey of Activities in Research, Education, and Therapy: III. The Status of Psychological Knowledge, Quart. J. Stud. Alcohol 13:444-452, 1952.

24. Williams, R. J.: Nutrition and Alcoholism, Norman, Okla., University of Oklahoma Press, 1951.

25. Popham, R. E.: Critique of Genetrophic Theory of Etiology of Alcoholism, Quart. J. Stud. Alcohol 14:228-237, 1953.

26. Lester, D., and Greenberg, L. A.: Nutrition and the Etiology of Alcoholism, Quart. J. Stud. Alcohol 13:553-560, 1952.

27. Smith, J. A.; Dardin, P. A., and Brown, W. T.: Quart. J. Stud. Alcohol 12:381-385, 1951.

28. Lang, T.: Zur Frage nach der genetischen Struktur von Homosexuellen und deren Eltern, Arch. Julius Klaus Stift. 20:51, 1945.

29. Beach, F. A.: Hormones and Behavior, New York, Paul B. Hoeber, Inc. (Medical Department of Harper & Brothers), 1948.

30. Goodale, H. D.: Note on the Behavior of Capons When Brooding Chicks, J. Animal Behavior 6:319-324, 1916.

31. Ellis, S.: The Sexual Psychology of Human Hermaphrodites, Psychosom. Med. 7:108-125, 1945.

32. Kretschmer, E.: Physique and Character, London, Routledge & Kegan Paul, Ltd., 1925.

33. Rees, W. L., and Eysenck, H. J.: A Factorial Study of Some Morphological and Psychological Aspects of Human Constitution, J. Ment. Sc. 91:8-21, 1945.

34. Sheldon, W. H.: Varieties of Delinquent Youth: An Introduction to Constitutional Psychiatry, New York, Harper & Brothers, 1942.

35. Sheldon, W. H.: Varieties of Temperament: A Psychology of Constitutional Differences, New York, Harper & Brothers, 1942.

36. Adcock, C. J.: A Factorial Examination of Sheldon's Types, J. Personality 16:312-319, 1948.

37. Lubin, A.: A Note on Sheldon's Table of Correlations Between Temperamental Traits, Brit. J. Psychol., Statist. Sect. 3:186-189, 1950.

38. Eysenck, H. J.: Dimensions of Personality, London, Routledge & Kegan Paul, Inc., 1947.

39. Lasker, G. W.: The Effects of Partial Starvation on Somatotypes, Am. J. Phys. Anthropol. 5:323-342, 1947.

40. Rees, W. L.: Physical Constitution, Neurosis and Psychosis, Proc. Roy. Soc. Med. 37:635-638, 1944.

41. Seltzer, C. C.: Body Disproportions and Dominant Personality Traits, Psychosom. Med. 8:75-97, 1946.

42. Cabot, P. S. de Q.: The Relationship Between Characteristics of Personality and Physique in Adolescents, Genetic Psychology Monographs, Vol. XX, No. 1, Provincetown, Mass., The Journal Press, 1938.

43. Fiske, D. W.: A Study of Relationships to Somatotype, J. Appl. Psychol. 28:505-519, 1944.

44. Kleinberg, O.; Asch, S. E., and Block, H.: An Experimental Study of Constitutional Type, Genetic Psychology Monographs, No. 16, Provincetown, Mass., The Journal Press, 1934, pp. 139-221.

45. Cattell, R. B.: Personality, New York, McGraw-Hill Book Company, 1950, p. 126.

46. Hall, C. S.: The Genetics of Behavior, in Handbook of Experimental Psychology, edited by S. S. Stevens, New York, John Wiley & Sons, Inc., 1951, Chap. 9.

47. Haldane, J. B. S.: Introduction to Biochemical Aspects of Genetics, Biochemical Society Symposia, edited by R. T. Williams, London, Cambridge University Press, No. 4, 1950.

48. Catcheside, D. G.: Gene Action and Mutation, in Biochemical Aspects of Genetics, Biochemical Society Symposia, edited by R. T. Williams, London, Cambridge University Press, No. 4, 1950, p. 32.

49. Penrose, L. S.: Garrod's Conception of Inborn Error and Its Development, in Biochemical Aspects of Genetics, Biochemical Society Symposia, edited by R. T. Williams, London, Cambridge University Press, 1950, No. 4, p. 10.

50. Kubie, L. S.: Some Implications for Psychoanalysis of Modern Concepts of the Organization of the Brain, Psychoanalyt. Quart. 22:21-68, 1953.

Malignant Tumors in Psychotic Patients

I. Studies of Incidence

OTTO F. EHRENTHEIL, M.D., Bedford, Mass.

The observation that malignant tumors are rare among patients in psychiatric hospitals has been reported frequently.* More recently, however, it has been contended that the frequency of malignant tumors is just as high among psychotics as in the general population and that the previous notion was based on a misleading statistical method.† However, the observations reported in both these groups of papers were based on mortality records, and it appears necessary to check the validity of the published opinions and conclusions by studying, in the setting of a large psychiatric hospital, the annual incidence of malignant tumors, that is, the number of cases first diagnosed during the study year. The present study is, as far as it could be ascertained, the first dealing with this aspect of the problem.

Present Investigation

During a three-year period from Dec. 31, 1951, to Dec. 31, 1954, a total of 46 cases of malignant tumors were discovered in this hospital. Included in this number are those cases in which a malignant tumor was suspected before Dec. 31, 1951, but in which the diagnosis was proved by biopsy, operation, or postmortem examination after this date.‡ Not included are those cases diagnosed only clinically before, but not yet proved histologically, on Dec. 31, 1954. Furthermore, patients admitted to the hospital with the diagnosis of cancer or admitted in the same year as the discovery of the malignant tumor were not included, since it was felt that the malignancy may have produced a deterioration of the total picture and may, in this way, have led to the hospital admission.

These 46 cases of malignant tumors occurred in 44 patients, two patients having independent cancers in two different sites. A breakdown of the data on the 46 malignant tumors is given in Table 1.

‡ To be exact, there were 45 cases in which the diagnosis of malignancy was proved microscopically and 1 in which it was not. However, this one case was included, as the patient showed metastatic carcinomatosis of the lung by x-ray and a subsequent intravenous pyelogram showed a kidney mass.

TABLE 1.—*Data on Forty-Six Malignant Tumors in Forty-Four Patients*

Site		Number
Genitourinary		13
Kidney	3	
Bladder	3	
Testicle (seminoma)	1	
Prostate	6*	
Gastrointestinal		12
Pharynx	1	
Esophagus	3	
Stomach	1	
Intestines (carcinoid)	1	
Colon	2	
Rectum	1	
Skin		11*†
Respiratory		5†
Larynx	1	
Lung	4†	
Miscellaneous		5
Plasma-cell myeloma	2	
Fibrosarcoma	1	
Perineural fibroblastoma	1	
Mucous membrane of lip	1	
Total		46

* One patient had a skin cancer and a prostatic cancer.

† One patient had skin cancers and a lung cancer; he had been operated on for skin tumors seven times: Epidermoid cancers of the skin were removed in 1947, 1948, 1949, and 1953; basal-cell cancers of the skin were removed in 1948 and 1952. In 1953 a primary lung tumor was found by x-ray and subsequently proved by autopsy.

Received for publication June 15, 1956.

From the Medical Service, Veterans Administration Hospital, Bedford, Mass., and the Department of Medicine, Tufts University Medical School, Boston. Physician, Medical Service, Veterans Administration Hospital; Clinical Instructor in Medicine, Tufts University Medical School.

* Reference 1, cited by Warren and Canavan.[3] References 2-6. Freeman, W., cited by Warren and Canavan.[3]

† References 7-10.

TABLE 2.—*Malignant Tumor Incidence Rates per 100,000 White Male Population and Expected and Actual Incidence in the V. A. Hospital, Bedford, Mass.*

1*	2†	3	4	5‡	6§	7
Age, Yr.	No. of Patients	Average Length of Hospital Stay, Yr.	Number of Patient-Years Observed	Annual Incidence Rate per 100,000 White Male Population	Expected Incidence in V.A. Hosp.	Actual Incidence in V.A. Hosp.
	During 3-Year Period 12/31/51 to 12/31/54					
15-19	14	0.6	8	25.0	0.0	0
20-24	103	0.8	84	25.4	0.0	0
25-29	285	1.6	455	35.5	0.2	0
30-34	454	1.9	866	62.7	0.5	1
35-39	336	1.8	609	96.3	0.6	0
40-44	175	1.8	311	169.4	0.5	0
45-49	121	1.8	214	271.6	0.6	1
50-54	151	2.0	315	516.0	1.6	0
55-59	512	2.4	1,215	816.9	9.9	14
60-64	375	2.4	898	1,208.2	10.9	12
65-69	149	2.4	358	1,532.9	5.5	11
70-74	26	1.8	47	2,107.3	1.0	2
75-79	21	2.3	50	2,643.9	1.3	3+(2)
80 & over	13	2.5	32	3,091.4	1.0	0
Totals	2,735	2.0	5,462		33.6	44+(2) 46 independent cancers in 44 patients

* Column 1: The age reference to a single year was necessary so that all patients could be included in one table. The ages of the patients are related to the year 1953, even though some patients may have died in 1952 or may have been admitted in 1954.

† Column 2: Each patient was counted only once, though he may have had a number of separate admissions to the hospital.

‡ Column 5: The annual incidence rate is the number of cases per 100,000 population first diagnosed during the study year. The figures are taken from U. S. Public Health Monograph No. 29: Morbidity from Cancer in the United States, 1935, p. 87, Government Printing Office, Washington, D. C.

§ Column 6: The figures for the expected incidence are arrived at by multiplying the number of observed patient-years by the incidence of cancer per 100,000 and then dividing the product by 100,000.

In Table 2 the incidence of newly discovered malignant tumors in the V. A. Neuropsychiatric Hospital, Bedford, Mass., is compared with the incidence found in the general white male population as reported in Public Health Monograph No. 29.§

Comment.—The reader may ask whether it is legitimate to increase the size of the sample by the device of using the case findings of three years for computing patient-years and to use these figures for determining the annual incidence rate. The answer is that this calculation is made possible by the fact that, insofar as the discovery of cancer is concerned, the patient can be considered as an "independent sample" each year; that is, the nondiscovery of cancer in a patient in one year does not influence the nondiscovery or the discovery of cancer in the same patient in the next year.

It may further be asked why the table for malignant tumors in the white male population was used. The answer is that the percentage of nonwhite patients in this V. A. hospital is on the average less than 3%. As the table for cancer in nonwhite men ‖ shows the incidence to be lower than among whites, a correction of the figure for the expected cancer incidence would have to be scaled slightly downward and the findings of this study would not change but, rather, would be more marked.

Analysis of the findings in Table 2 revealed that there is no significant statistical difference in the incidence of cancer in the two populations. The apparent higher figure in the psychotic population is very likely due to the closer medical observation given to patients in a V. A. Psychiatric Hospital than in the general population. Thus, it is apparent that the result of this study is contradictory to many statements in the literature (see "Comment") which held that cancer is rare among psychotics.

§ Dorn and Cutler,[11] p. 87.

‖ Dorn and Cutler,[11] p. 89.

General Comment

The findings and conclusions of this investigation, namely, that no difference exists in the incidence of malignant tumors in psychotic and in the general population appear to be especially interesting when they are compared with findings and conclusions previously reported. Most writers on this subject had used for their investigations the proportionate mortality rate, and the results of their studies will be summarized briefly.

In the report for 1909 of the Commissioners in Lunacy for England and Wales,[1] it is stated "There remains one morbid condition (cancer) which is responsible for an increasing number of deaths in the general community from which it would almost appear as if the insane enjoyed some immunity." Warren and Canavan[2] cite in their paper a number of authors ¶ who reported a low incidence of cancer mortality among psychotics. The number of cancer deaths found in mental institutions was only one-third the number in the general population. Warren and Canavan's own investigation was based on legal autopsies in a period of 20 years performed in cases of sudden or unexpected death at various state mental hospitals. They reported among 2627 autopsies 114 cases of cancer, or an occurrence of 4.3%. They consider this figure extremely low, and their findings seemed to be in agreement with those of other authors (Hahnemann,[3] Chevens,[4] Lind,[5] Lombard,[6] Freeman,# and others). As a result of their investigations, Warren and Canavan[2] speculate that "evidence is accumulating that a constitutional predisposition to cancer, perhaps hereditary, exists. Heredity may also be of importance in insanity. We must at least consider the hypothesis that the soil best suited for the development of cancer differs from that in which insanity develops."

As opposed to this statement, there are reports in the literature noting the occurrence of malignant tumors in psychotic patients to be not smaller than, but just the same as, that in the general population (Opsahl,[7] Copeman and Greenwood,[8] Peller and Stephenson[9]). Scheflen[12] discussed this controversy and showed that the two groups of investigators used two different statistical methods. The proportional mortality rate for cancer shows how often cancer is found in the autopsy material, and this proportion was always found to be low in a psychiatric hospital. This, according to Scheflen, gives misleading results. He pointed out that in Massachusetts the annual death rate was about seven times as great in the institutionalized psychotic population as it was in the general population. This higher death rate of psychotics obtained elsewhere in the United States and in the British Isles. Scheflen then stated:

> Populations can be compared for specific causes of death on the basis of proportionate mortality rates only when they have equal or nearly equal death rates. In other words, if the members of one population are dying seven times as fast of tuberculosis, for instance, as those of another, they will not survive to die of cancer. Proportionate mortality rates, based on the total deaths, are dependent, then, on the death rate from all other conditions.

The same explanation was given by Peller.[10] According to him, dementia paralytica, tuberculosis, alcoholism, and suicide are so much commoner in mental hospitals than in the general population of similar age distribution that even a higher cancer incidence and mortality are compatible with a diminished ratio of cancer in proportion to all other deaths. If, however, the number of cancer deaths is viewed in relation to the number of psychotic patients in the particular age group (Peller), there seems to be almost no difference between the psychotic and the nonpsychotic population (cancer death rate in contradistinction to proportional mortality rate for cancer). Scheflen[12] has tried to establish the cancer death rate for the Worcester State Hospital by studying the records of all patients who died there from 1928 to 1942. He found (a computed series of) 295 cases of

¶ References 3-6. Freeman, W., cited by Warren and Canavan.[2]

Cited by Warren and Canavan.[2]

death from malignant tumors, in 144 of which autopsy was performed. These deaths occurred among 55,000 patient-years (number of patients multiplied by the period of hospitalization). On the basis of his research, Scheflen came to the conclusion that "the opinion that cancer is rare in psychiatric hospital patients, relatively or absolutely, does not seem justified."

The results of my own studies are in agreement with Scheflen's and Peller's findings and were arrived at by another statistical approach, namely, the annual incidence rate. This latter method has the great advantage that less unproved assumptions are necessary. Scheflen made the assumption that the occurrence of cancer in the cases of death without autopsy was proportionately the same as in the cases with autopsy. This assumption is probably correct, but it can be neither proved nor disproved. No such assumption was necessary in computing the incidence rate in our hospital. Last, but not least, the incidence and prevalence rates are much closer to the daily work of the clinician than are statistics based on mortality rates. I was more fortunate than the previous authors in having at my disposal the monograph of the U. S. Public Health Department on the morbidity from cancer.

Incidence of Malignant Tumors in the Various Psychiatric Diagnostic Groups

The fact that no difference exists between the incidence of cancer in the psychotic and that in the nonpsychotic population still leaves open the question of whether a differential incidence exists among the various psychiatric diagnostic groups. This question requires examination, since quite a number of investigators * reported a higher occurrence of cancer in paranoid patients than in patients with hebephrenic and catatonic schizophrenia. However, since these studies were based on mortality statistics, it appears to be of interest to determine whether the described difference is also found when the study dates are based on microscopically verified newly diagnosed cases and not on mortality statistics.

Table 3 lists all the cases of malignant tumors and shows the age of the patients, their psychiatric diagnoses, and the site of the tumor. The data in this Table become more meaningful when they are seen in relation to the distribution of the male Bedford hospital population grouped according to age and psychiatric diagnosis. This is done in Table 4, for the hospital population as of June 30, 1953.

Using the information in Table 4 and the cancer incidence rates for the white male population given in U. S. Public Health Monograph 29,† we arrive at the following findings:

1. In 1509 observed patient-years in the paranoid group, the expected incidence of malignant tumors was 7.4 and the actual incidence was 10 (in 9 patients).

2. In the combined group of catatonics and hebephrenics were 2208 patient-years, and the expected incidence of malignant tumors was 12.1 and the actual incidence 13 (in 12 patients).

3. In the combined groups of patients with the catatonic, hebephrenic, simple, and undetermined types of schizophrenia (all the schizophrenics except the paranoids), we find for a total number of 2871 observed patient-years an expected incidence of 15.0 malignant tumors and an actual incidence of 20 (in 19 patients). Thus, on the basis of the admittedly limited experience of the tumor clinic of our hospital, no evidence has been found which supports the contention that the incidence of malignant tumors in schizophrenics is greater in the paranoid than in the nonparanoid type.

Summary

The problem of the occurrence of malignant tumors in psychotic patients, which previously had been studied by using mortality data, was investigated by determining the annual incidence.

* References 12-15.

† Reference 11, p. 87.

TABLE 3.—*Malignant Tumor Cases According to Age, Site, and Psychiatric Diagnosis*

Site	Age Group										Psychiatric Diagnosis										
	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	P	C	H	S	A1	Dp	Ar	T	D	Aff	Total
Buccal cavity							H						1								1
Digestive system						PP SS	Aff A1S	A1 CSD	Ar		2	1		4	2		1		1	1	12
Respiratory system							Dp	PT	Ar	H	1		1			1	1	1			5
Male genitals	P					SDp	C	H		ArP	2	1	1	1		1	1				7
Urinary system						PC HS	PH				2	1	2	1							6
Skin				P		CC Dp	PH	A1 A1A1		**PH**	2+1	2	1+1		3	1					9+2
Soft tissue							A1								1						1
Lymphoma						H	A1						1		1						2
Other sites								S						1							1
Diagnosis																					
Paranoid (P)	1			1		3	2	1		1+1											9+1
Catatonic (C)						3	1	1													5
Hebephrenic (H)						2	3	1		1+1											7+1
Simple & others (S)						4	1	2													7
Alcoholic (A1)							3	4													7
Dementia paralytica (Dp)						2	1														3
Arteriosclerosis (Ar)									2	1											3
Brain Trauma (T)								1													1
Brain atrophy (D)								1													1
Affective psychoses (Aff)							1														1
Totals	1			1		14	12	11	2	3+2	9+1	5	7+1	7	7	3	3	1	1	1	44+2

The two instances in which the symbols are in bold face represent patients with skin cancers in whom also an independent internal cancer was found.
There were no patients with cancers of the following sites: breast; brain; endocrine; bone; leukemia.

TABLE 4.—*Male Patients by Age and Mental Disorder as of June 30, 1953*

Diagnosis	Totals	Percentage	Under 20	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	Over 80
Schizophrenic reaction																
Paranoid type	503			2	37	92	67	54	31	25	86	76	26	1	6	
Catatonic type	374		1	7	62	99	55	17	10	18	59	33	12			1
Hebephrenic type	362			2	10	35	29	14	10	42	114	81	20	2	3	
Other types	166			6	27	48	28	10	7	3	20	11	3	3		
Simple type	55				1	6	6	2	2	3	19	8	6	2		
Total schizophrenics	1460	79.6	1	17	137	280	185	97	60	91	298	209	67	8	9	1
Chronic alcoholics with psychotic reaction	77	4.2						3	3	2	25	22	17	1	1	3
Syphilis with psychotic reaction	99	5.4				1		1		6	47	32	12			
Organics with psychotic reaction	82	4.5			4	6	9		5	5	13	15	16	3	4	2
Affective psychoses	49	2.7			1	1	4	3	1	2	18	9	4	2	4	1
Miscellaneous psychotics	33	1.8				3	2		2		9	13	4			
Nonpsychotics	34	1.8		2	3	4	7	3	3		5	4	3			
Total	1834	100.0	1	19	145	295	207	106	74	106	415	304	123	14	18	7
Percentage	100.0		0.05	1.0	7.9	16.1	11.3	5.8	4.0	5.8	22.6	16.6	6.7	0.75	1.0	0.4

Contrary to the conclusions of some previous studies, it was found that no significant difference exists between the incidence of malignant tumors in psychotics and that in the general population.

On the basis of an admittedly small sample, it was found that the occurrence of cancer among paranoids and that among other schizophrenic groups does not seem to be different.

Results of investigations based on the proportionate mortality rate and on the annual death rate from malignant tumors among psychotics are discussed and compared with the results of this study.

Miss Ann Kelley, the Medical Records Librarian of the V. A. Hospital, Bedford, Mass., helped in compiling the statistical data.

REFERENCES

1. Report of the Board of Control of the Commission of Lunacy for England and Wales, for 1909.

2. Warren, S., and Canavan, M. M.: Frequency of Cancer in the Insane, New England J. Med. 210:739-742, 1934.

3. Hahnemann, V.: Cancer Mortality and Mental Diseases, Ugesk. læger 93:1132-1139, 1931.

4. Chevens, L. C. F.: Correlation of Causes of Death with Type of Insanity, J. Ment. Sc. 77:562-577, 1931.

5. Lind, W. A. T.: Cancer and Chronic Insanity, M. J. Australia 2:378-379, 1928.

6. Lombard: House Document No. 1200, Commonwealth of Massachusetts, Boston, 1925.

7. Opsahl, R.: Frequency of Cancer Among Patients with Mental Diseases, Norsk mag. lægevidensk. 94:771-790, 1933.

8. Copeman, S. M., and Greenwood, M.: Ministry of Health, Great Britain, Publication No. 36, 1926.

9. Peller, S., and Stephenson, C. S.: Cancer in Mentally Ill, Pub. Health Rep. 56:132-149, 1941.

10. Peller, S.: Cancer in Man, New York, International Universities Press, 1952.

11. Dorn, H. F., and Cutler, S. J.: Morbidity from Cancer in the United States: I., U. S. Public Health Monograph No. 29, U. S. Department of Health, Education, and Welfare, 1955.

12. Scheflen, A. E.: Malignant Tumors in Institutionalized Psychotic Population, A. M. A. Arch. Neurol. & Psychiat. 66:145-155, 1951.

13. Lewis, N. D. C.: Research in Dementia Praecox: Past Attainments, Present Trends, Future Possibilities, New York, National Committee for Mental Hygiene, 1936.

14. White, W. A.: The Social Significance of Mental Disease, Arch. Neurol. & Psychiat. 22:873-900, 1929.

15. Sheldon, W. H.; Stevens, S. S., and Tucker, W. B.: The Varieties of Human Psysique, New York, Harper & Brothers, 1940.

Activation of Psychosis by a Combination of Scopolamine and Alpha-Chloralose

RUSSELL MONROE, M.D.
GEORGE JACOBSON, M.D., New Orleans
and
FRANK ERVIN, M.D., Mandeville, La.

The investigation of physiologic concomitants of disturbed behavior has been of interest for many years. In particular, the use of the EEG has been emphasized since the days of Hans Berger, and some meaningful correlations have been made in the case of "psychopathic" or aggressive behavior disorders. The value of the EEG in recognizing epilepsy and epileptic equivalents is common knowledge. However, in spite of much work on psychosis and a fairly widespread agreement that there is a "higher incidence" of EEG abnormalities in hospitalized psychotic patients than in the general population, little other meaningful correlation has been noted. For a good review, Ellingson [6] may be referred to. Interest in this subject has been renewed in recent years by the description of subcortical electrophysiologic abnormalities in psychotic patients by Heath, Sem-Jacobsen, Delgado, and others. These investigations have raised the question as to whether there is in some or all psychotic patients a coincident neurophysiologic dysfunction which can be consistently demonstrated. If such an abnormality could be demonstrated in at least a subgroup are psychotic patients, an important clue might be afforded the further investigation and more rational therapy of schizophrenia and other psychoses.

That there is correlation between disturbed cerebral function and behavioral abnormality has long been emphasized in the case of the psychomotor epileptics, whose complete seizures may well resemble psychotic states, as Hughlings Jackson clearly recognized. More recently, Ervin, Epstein, and King * have pointed out the high incidence of a personality disorder often similar to schizophrenia in patients in whom temporal spike abnormalities were present in the EEG, whether or not they had frank psychomotor seizures. Similar observations have been made by Hill [10] and others.

The possibility of electrophysiologic dysfunction in the schizophrenic (not ordinarily detectable on the EEG) raises the question of whether proper activation might make it detectable, as is often the case in epilepsy. Our attention was drawn to a report by Bercel [3] suggesting the use of a mixture of scopolamine and α-chloralose (SAC) for the activation of the EEG in epileptics. In his small group of patients, all three with psychomotor epilepsy became acutely psychotic under this drug combination. He states this was not a typical psychomotor seizure. The French literature had emphasized the value of this drug combination in activating epileptic records, particularly because it did not produce clinical seizures (Baruk [4]). A recent article by Verdeaux and associates [14] reported on a group of 124 patients with "doubtful spells, character disturbances, impulsive behavior, or psychasthenic symptoms," whom they compared with 121 patients with overt epilepsy.

Received for publication June 12, 1956.

Department of Psychiatry and Neurology, Tulane University School of Medicine (Dr. Monroe and Dr. Jacobson). Research Unit, Southeast Louisiana Hospital, Mandeville, La. (Dr. Ervin). Aided in part by research grant from The Commonwealth Fund.

* References 7 and 8.

In this group of patients he noted that hypersynchrony and/or the appearance of spikes was the characteristic effect on the electroencephalogram. In 73 psychiatric patients, hypersynchrony appeared 48 times and was described as the characteristic of this group. The epileptic group, on the other hand, commonly showed spikes (except in cases of petit mal, where definite spike-and-dome complexes appeared). This author did not note behavioral changes in detail, although he did mention "states of satyriasis, confusional states, and certain psychic manifestations that French psychiatrists call larval epilepsy of Morel."

An earlier paper by Monroe and associates [11] describes the effects on the EEG of the first 30 psychiatric cases in our group given this drug. The common effect on the EEG was slowing and slight build-up in amplitude of the record. The most frequent change in the patient group was the appearance of paroxysmal, high-amplitude, hypersynchronous discharges, usually of a slow-wave type, which were either focal or generalized. Some patients showed, in addition, focal or generalized spike discharges, and a few patients showed only isolated spikes in response to the activation.

The physiologic basis of the EEG effect of SAC is not clear. Choralose has long been used as a laboratory anesthetic, and one of its characteristics is its both depressing and stimulating action on the central nervous system. For example, on peripheral sensory stimulation in animals, the evoked secondary response is suppressed in the cortical sensory receiving area while the primary response becomes exaggerated. It has also been noted that in animals under chloralose anesthesia a light tap on a limb may precipitate a motor seizure, as in the strychninized animal. The general impression is that chloralose produces an extreme facilitation of cortical responses while inhibiting other, particularly brain stem, responses, and indeed producing anesthesia. Gestaut [5] has emphasized the double, apparently parodoxical effect of chloralose on cerebral excitability, demonstrating the lengthening of the cycle of excitability of the cortex seen with all anesthetics, including the barbiturates, but coincidentally the increase in the amplitude of the cycles, similar to that produced by convulsive substances (pentylenetetrazol [Metrazol]). That the excitatory effect is primarily in the cortex is suggested by some work of Moruzzi,[5] who has demonstrated that the excitatory effect is abolished by decerebration in mammals and does not appear in pigeons, who have little cortex (see also Rosenblueth and Cannon [13]). As both sleep and stimulants are used clinically for EEG activation, it is not surprising that a drug with the combined properties described above would be a potent activator.

Because of these interesting physiologic properties, it was felt that administration of scopolamine-α-chloralose with simultaneous behavioral and EEG observations might prove a fruitful research technique. The purpose of this project was to investigate (1) whether there was a specific group of psychotic patients in whom the administration of SAC would produce EEG abnormalities; (2) whether behavioral disturbances could be produced in a significant number of psychotic patients; (3) whether the behavioral disturbances induced correlated with specific EEG abnormalities, and to what extent the behavioral changes were similar to the patient's spontaneous symptoms, rather than a simple toxic effect of the drug, as seen in alcohol or bromide intoxication, or some new pattern of disturbance, such as that produced by lysergic acid diethylamide (LSD) or mescaline, and (4) whether there was a specific symptom complex characteristic of those patients activated which would allow their recognition as a clinical diagnostic group.

Method

The technique of chloralose activation in our studies was similar to that employed by Bercel.[3] All the patients had had a previous routine EEG. A 10- to 15-minute base-line EEG recording was made on the day of the experiment, including at least one 3-minute period of hyperventilation. Scopolamine-α-chloralose was dissolved in water

and given by mouth. EEG recordings were started with hyperventilation every 15 or 30 minutes. Records were followed for as long as two to three hours, or until maximal EEG abnormalities appeared. In some patients, follow-up studies were done during the next 24 hours. Also, pulse rates were taken as an additional method of following the effectiveness of the chloralose. Side-effects were essentially those reported in the original study.[12]

In all of the subjects, both volunteers and patients, a combination of 500 mg. of chloralose and 0.5 mg. of scopolamine hydrobromide was used. When the study was begun, this combination of drugs was the only available product that contained pure α-chloralose. Recently, however, α-chloralose has become available, and it is planned to use this preparation in the future, since comparative studies reveal that scopolamine has no potentiating effect as far as behavioral or EEG changes are concerned.

The experimental set-up included an EEG room with one-way mirrors so that the subject could be under constant observation. One of us or an EEG technician was always in attendance. The standard technique for electrode applications to the scalp and the EEG recordings was used. A brief mental-status examination was usually performed at the beginning of the test and again at the end. In addition to this, the patients were encouraged to be spontaneous in reporting of symptoms, feelings, thoughts, or sensations during the test period, but no direct questions were asked. At the end of the study, the subjects were carefully questioned about specific changes in affect or thought content, particularly regarding the appearance of symptoms spontaneously occurring in the past. If these were reported only on direct questioning, their validity was carefully weighed.

The control series consisted of 31 subjects. The first 15 were primarily laboratory workers, physicians, and other personnel connected with the project. Of these 15 subjects, 4 showed borderline EEG abnormalities during the base line which were intensified on activation through the administration of chloralose. The second group of volunteers consisted of 16 subjects, mostly nurses, medical students, secretaries, etc., and, of these, 3 showed borderline abnormalities in the base-line EEG. It is interesting to note that the second group of volunteers were primarily "solicited volunteers," who worked either in the medical school or at the hospital used in conjunction with the study. They showed a high incidence of emotional problems, many attending the outpatient psychiatric clinic; and there was a high incidence of previous head injury or neurologic disorder in this group. Many were obviously motivated to volunteer to "find out more about themselves." This group was a dramatic reminder of the importance of distinguishing between "controls" and "volunteers," particularly in psychological investigations.

Half of the neurology patients had a proved diagnosis of focal cortical disease on clinical, laboratory, or operative examination. In two cases only equivocal findings were present on neurologic examination. The other neurologic patients were a group of suspected epileptics for whom careful hospital work-up, including routine EEG's, had failed to clarify the diagnosis and for most of whom the EEG was normal or borderline.

The psychiatric patient group is not a cross section of a usual hospital population, since many of the early cases examined had marked impulsive or "episodic" behavior, although later cases were selected at random. Our hospital population also contained many patients diagnosed as schizophrenic, although no secondary symptoms of delusions or hallucinations had ever been present. This weighted patient sample probably accounts for the higher incidence of base-line EEG abnormality than is usually seen and may produce a higher per cent of activation with SAC than a chronic hospital population would show. No patients or volunteers over 50 or under 17 years of age were used. All of the psychiatric patients had neurologic work-ups and routine skull x-rays.

Results

Electroencephalographic Findings.—Figures 1 and 2 summarize the experimental findings; however, certain important details need elaboration. Of the 15 neurologic patients who have proved central nervous system lesions, 13 showed focal activation on the side of the lesion (if it was lateralized) after the administration of SAC. This occurred despite the fact that eight had either normal or borderline EEG's during routine electroencephalographic studies.† The two who did not show activation had minimal localizing signs and symptoms, with no x-ray or operative evidence of focal lesion. The 16 epileptics reported all had minimal symptoms and signs, and 13 of the 16 had normal or questionable electroencephalograms during the usual routine recording. It is to be noted that after SAC 15 of the 16 had defi-

† By borderline EEG we mean slight build-up on hyperventilation with immediate return to normal, questionable amplitude asymmetry, slightly slow or fast records, or questionable focal or random spikes.

Experimental Gp.		Baseline EEG			Activated EEG			Behavioral Responses					
	Sub-Group	Normal	Borderline	Abnormal	Normal	Borderline	Abnormal	Relaxation	Minimal change in behavior	Clouding of sensorium	Seizure	Recurrence of discrete symptoms	Psychotic behavior
Volunteers	Without personality disorder (19)	16	2	1	13		6	14	2	3			
	History of neuro. complication (4)	2	2				4	2	2				
	With known personality disorder (8)	3	2	3	1		7	3	4				1
Total = 31		21	6	4	14		17	19	8	3			1
Neurologic Patients	Focal lesion (15)	2	7	6	2		13	11	3	1			
	Epilepsy (16)	11	2	3	1		15	8	3	1	2	1	1
Total = 31		13	9	9	3		28	19	6	2	2	1	1
Psychiatric Patients	No drugs (44)	23	8	13	10	1	33	12	10	2		2	18
	On drugs (21)	14	5	2	5	1	15		13	2			6
Total = 65		37	13	15	15	2	48	12	23	4		2	24

Fig. 1.—Summary of reactions to scopolamine-α-chloralose (SAC).

nite evidence of EEG abnormalities compatible with the clinical diagnosis. A detailed report of these patients is now in preparation, but they are mentioned here to support the concept that the paroxysmal hypersynchrony or spiking activity seen after administration of SAC is an augmentation of a real potential for this type of physiologic response. This concept is also supported by the consistent augmentation of any slight abnormality in the EEG in all groups studied. If this is true, it is striking that of the 65 psychiatric patients 48 should show definite paroxysmal electroencephalographic activity after the administration of SAC, although only 15 had any abnormalities during routine electroencephalograms. This group of 48 patients does not include those who showed mild generalized slowing in the record, which we feel is characteristic of the toxic effects of SAC. (This effect can be elicited in normals who have not shown activation with the usual dose of 500 mg. if the dose is raised to a toxic level.) To us this suggests that in a large group of severely disturbed patients, one of the physiologic abnormalities heretofore not conclusively demonstrated is this tendency toward cortical hypersynchrony (Hill [10]).

Our small group of volunteers, however, showed a high incidence of similar activity, with 17 of 31 demonstrating paroxysmal hypersynchrony after SAC. However, detailed reinvestigation of the group revealed that in eight volunteers detailed psychiatric and psychological studies in the departmental outpatient clinic done prior to this study showed evidence of severe personality disorder, with a diagnosis of probable psychosis. Four others had a good history of central nervous system complication; three, of severe head trauma; one, of migraine. In this particular group of 12 volunteers, 11 showed activation. Only 3 of the 19 in the group who did not have evidence of disturbed behavior or a borderline base-line EEG were similarly activated. It is obvious from the above that a carefully screened

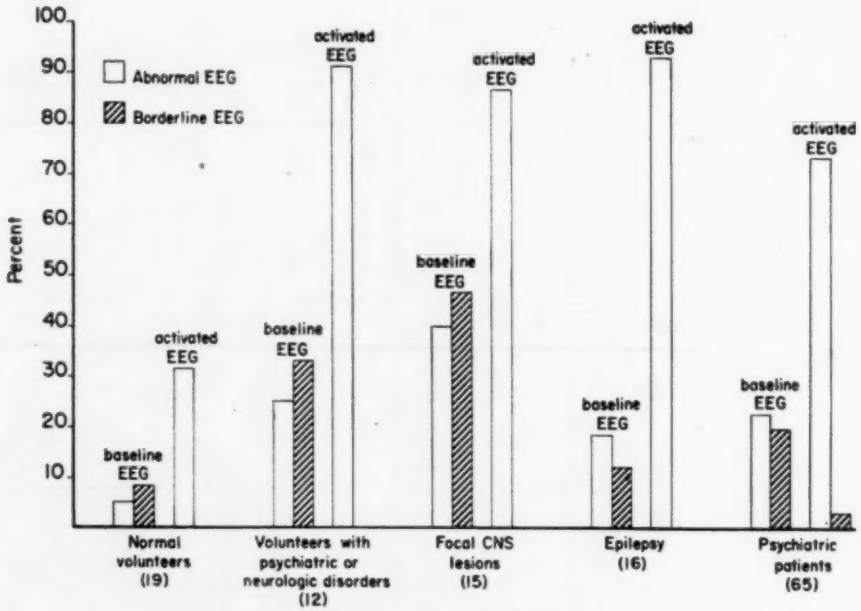


Fig. 2.—EEG responses to activation.

group of volunteers is needed to serve as "normal controls."

In agreement with Baruk,[4] we found that, despite this CNS activation, only 3 of the 127 subjects had actual seizures. Two had psychomotor seizures associated with automatic movements, bizarre behavior, clouding of sensorium, and amnesia; the other lost consciousness and had occasional myoclonic jerks in the upper extremities, which could be aggravated by passive movement, after the onset of psychotic behavior. She responded readily when 4 grains (0.25 gm.) of phenobarbital sodium was given intravenously, regaining consciousness immediately.

Behavioral Response.—The SAC used in this study is marketed in Europe as a sedative.‡ The usual clinical response is a sense of lassitude, even weakness, indifference, and light sleep. Other effects are minimal behavioral changes (Fig. 1), such as loss of inhibition, mild euphoria, expression of warm, dependent needs, sometimes slightly seductive behavior, and occasionally excessive gaiety or silliness. Accompanying this response there may be minor motor changes with myoclonic movements, particularly in the hands, aggravated by spontaneous or passive movement in the extremity. There may be a slight ataxia, and occasionally a positive Romberg sign, dizziness, and weakness.

Of the 127 patients who took medication, 9 showed a severe organic type of reaction. This was marked by clouding of sensorium with disorientation, memory loss, and perseveration, followed by amnesia. In many others of the experimental group, mild difficulties in finer intellectual performance, such as complicated calculations, awareness of the passage of time, or quick response to questions of orientation and recent memory, could be elicited, as well as slight vagueness in recalling the experience. However, as reported below, the clouding of sensorium was not in any way proportionate to the disturbed behavior shown in those that had a psychotic reaction.

‡ Kuhlmann, Paris.

Activation of Psychotic Behavior.—Of the 48 psychiatric patients with EEG activation, 24 showed evidence of psychotic reactions, as described below (Fig. 3). In

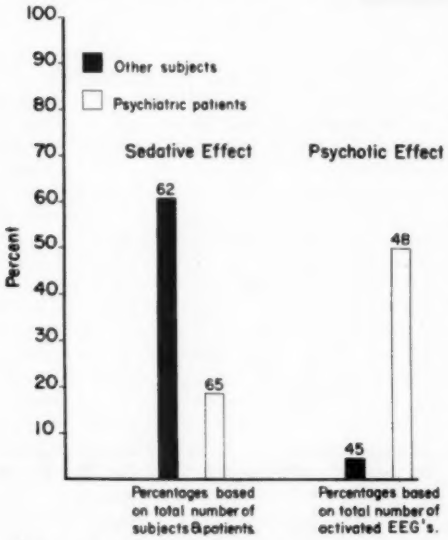


Fig. 3.—Behavioral responses to activation.

every instance this was accompanied by paroxysmal hypersynchrony, although not correlated with the degree of EEG change. Many patients showed the paroxysmal hypersynchrony without evidence of psychotic behavior. Of the 62 subjects, who included the volunteers and the neurologic patients, 45 showed EEG activation but only 2 demonstrated psychotic reactions. One became agitated, confused, depressed, and suicidal, had persistent vomiting, and showed hysterical acting out, requiring overnight hospitalization. A subsequent detailed medical history revealed that similar reactions had occurred on two occasions in the past when she had general anesthesia. The other, a neurologic patient with grand mal and psychomotor seizures, was actually hospitalized on the psychiatric service at the time because of the bizarreness of these seizures. He was of borderline intelligence but did not demonstrate psychotic behavior except during ictal states; he, therefore, was included in the neurologic group. Although he was oriented under the drug, he hallucinated a vision of his girl friend, talked with her, and tried to get up from the bed to hug her. The low incidence of psychotic behavior in those patients who have not in the past shown similar behavior spontaneously suggests that the phenomenon induced by SAC is not similar to the specific psychosis-inducing effect of LSD or mescaline. Moreover, normals who have shown no evidence of EEG activation or psychotic behavior under the drug, but who have taken high doses of SAC, show the toxic phenomenon of sleepiness, confusion, and disorientation, with amnesia, but no psychotic behavior. This supports the concept that SAC behavioral activation reflects an activation of true psychological potentiality for psychotic behavior. Figures 2 and 3 summarize in graphic form both the EEG activation and the behavioral activation of the experimental group under SAC.

In the group of 26 patients who showed psychotic behavior (Fig. 4) a predominant reaction was acting out of sexual, angry, or fearful impulses, which occurred in 14 cases; 12 complained of feelings of unreality or depersonalization; 9 had definite fear and rage reactions not accompanied by acting out; 9, depressions, while only 3 had overt hallucinations and 2 delusions; 6 showed extensive confusion, which was not just clouding of sensorium; only 2 had severe disorientation, and 3 had complete amnesia for the experience.

In view of the predominance of acting out and depersonalization manifest under the SAC and the fact that the overtly psychotic behavior was frequently similar to the spontaneous behavior shown by the patient (in 22 of the 26 patients), it was felt that this drug might differentiate a group of patients characterized by impulsive acting out of an episodic nature. Of the 26, 16 had definite evidence of impulsive behavior, and 19 showed episodic behavior disorders. Of the remaining experimental subjects who were psychiatric patients but who did not show psychotic behavior under the influence

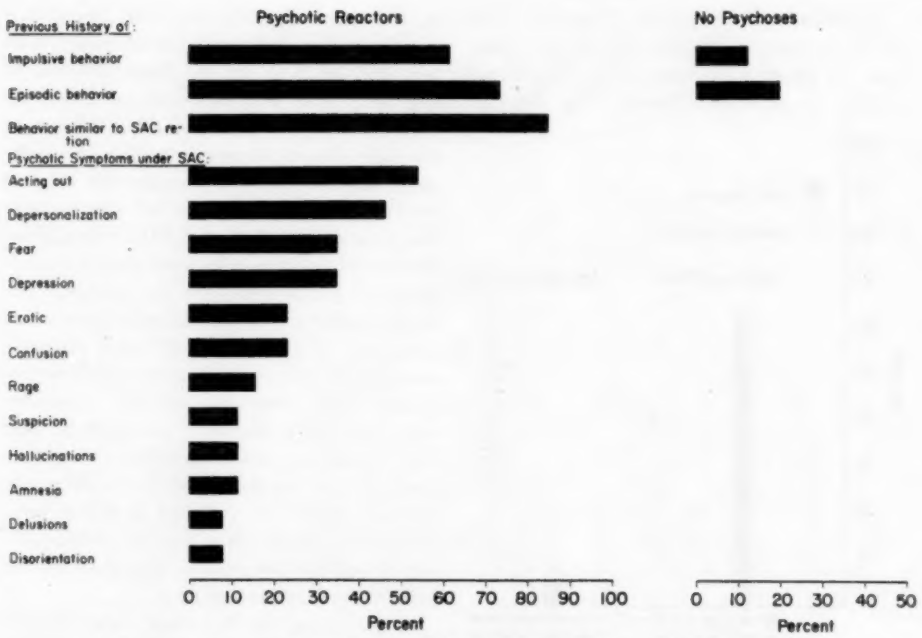


Fig. 4.—Summary of psychotic reactions to scopolamine-α-chloralose (SAC).

of this drug, only 5 out of 41 had histories of impulsive behavior, while 8 out of 41 had a history of episodic disturbances. It is interesting to note that approximately half of the psychiatric patient group was routinely taking one or another "ataractic" drug at the time of the test. There was no apparent effect on EEG changes, and probably no reduction in the psychosis-inducing potential of this procedure. It would seem from the above that the SAC activation of psychotic behavior does occur in those who are predisposed to this type of behavior. This observation has certain implications in terms of the mechanism of episodic psychotic episodes and possible choices for treatment.

Correlation of Behavioral and EEG Activation.—In this extended series, the correlation noted by Monroe [11] in the original study was not as precise. As would be expected, when the patient reported drowsiness or sleep, there were typical drowsy or sleep recordings on the EEG. High-amplitude generalized slow activity was often associated with markedly confused behavior, but other patients would show slowing to a similar degree without the confusion. Of the 26 subjects who manifested psychotic behavior under the influence of this drug, 9 had both paroxysmal or high-amplitude theta-delta and spiking activity, which might be generalized or localized. Only three in this group had moderate generalized slowing alone. The remainder presented high-amplitude, paroxysmal theta or delta activity, which might be focal, show a shifting focus, or ultimately become generalized and continuous. Thus, at the moment, we can make no specific correlation between scalp recordings and the various types of behavioral changes. As reported in the previous study,[11] nine patients with subcortical electrodes in at least the septal, hypothalamic, and hippocampal region, as well as on the cortex, have not helped in making correlations between behavior and electroencephalograms.

Report of Case

To clarify the type of patient most likely to show both the electroencephalographic and

the behavioral activation under SAC, we would like to present in detail one case history, accompanied by a discussion of the similarities and differences in those patients who showed no electroencephalographic activation after the administration of SAC.

A 27-year-old housewife, a mother of two mentally retarded children, was admitted to the hospital in February, 1945, for evaluation and treatment of episodic psychotic reactions, lasting from a few hours to a few weeks, and severe enough on six occasions to require hospitalization or incarceration in jail. These episodes, described as "spells" by her husband, were preceded by mounting irritability, hypochondriasis, and severe occipital headaches. As the attack progressed, there would be withdrawal and lack of emotional response, accompanied by a staring, vacant look in the eyes; this would be followed by outbursts of rage and destructiveness, at which time the patient would be physically abusive toward her husband or children, or self-mutilative, and, in fact, on two occasions suicidal. These "spells" would be accompanied by visual hallucinations, particularly of her children cringing in fear, or at other times of her mother, husband, and children calling her names and admonishing her. She would break up furniture, tear off her clothes, and try to tear her hair "to get the snakes out of it." These attacks would be accompanied by varying degrees of confusion and disorientation. Although she claimed complete amnesia for the episodes, detailed questioning revealed that there was generally some hazy recollection. Following the attack, there would be a period of depression and remorse. Amobarbital (Amytal) sodium intravenously would often control the behavior and sometimes abort the attacks. At other times hospitalization was required for as long as two months, with the patient receiving EST and subcoma insulin. During the intervals between these attacks, the patient was hostile and irritable, constantly taunting her husband about past mistakes and suspiciously accusing him of extramarital affairs, whereas she herself was occasionally promiscuous. She had constant hypochondriacal complaints, which led to frequent visits to her doctor and several hospitalizations with two laparotomies.

The patient is the oldest of five children, the others being boys, born into a family of low economic and social status. The emotional climate of the home was unstable. The father, who apparently was affectionate toward the patient and gave her some emotional security, was described, nevertheless, as an alcoholic who was irresponsible and frequently away from home philandering. On the other hand, the mother, who was reliable and supported the family, was described as having a personality much like the patient's, being particularly hostile and restrictive toward the patient, while favoring the boys. The mother never allowed the patient to socialize freely, and during adolescence restricted her social activities, while accusing her unjustly of sexual promiscuity. She conveyed to the patient her own suspiciousness and sense that the world was a hostile place.

The patient says of herself, "I was always different and confused." She was shy and isolated, while quick-tempered and belligerent, rebelling against authority and fearful of school. She had numerous phobias, particularly concerning darkness and fire. The latter had some realistic basis, since, at the age of 3 years, she sustained severe third-degree burns over her body and face, requiring repeated plastic surgical operations, which had left her face considerably scarred and distorted. She was attached to her father but furious about his philandering, with her anger directed toward the girl friends more than toward the father himself. However, after her father's divorce and subsequent marriage, she accepted both her father and his wife, often expressing a desire to go and live with them. Her childhood and adolescence were characterized by isolation, and only superficial emotional relationships with peers or family. She met her husband in the hospital while undergoing a plastic operation, married him shortly thereafter, and had difficulties in adjusting to the marriage from the start. Sexual adjustment was always poor, with the patient failing to attain orgasm until the last year or so. Attempts at coitus, as well as her pregnancy and delivery, were accompanied by much acting out of the aggressive behavior described above.

Aside from the scarring on the face, hands, and trunk, physical and neurologic examinations were noncontributory. Laboratory findings were all negative except for the electroencephalogram, which showed some short runs of 6, 7, and 7½ per second activity and a small build-up on hyperventilation, with immediate return to normal. The record was read as a generalized slightly slow record, consistent with, but not indicative of, epilepsy.

At the time of admission to the hospital, the patient was somewhat irritable and suspicious but otherwise cooperative, showing no evidence of the episodic behavior described above. Intellectual testing and a routine mental status examination revealed no abnormality. However, during the course of her hospital stay, she would show the typical "spells," which would generally last for 24 hours, but might persist for weeks. Attempts to control the behavior with anticonvulsants, such as diphenylhydantoin (Dilantin), phenobarbital, and trimethadione (Tridione), were unsuccessful, as were reserpine and chlorpromazine. The behavior could

best be aborted by amobarbital sodium 7½ grains (0.5 gm.) intravenously, followed by maintenance doses of 3¾ grains (0.25 gm.) by mouth or intramuscularly three times a day.

This type of patient presents a real diagnostic problem, not fitting descriptively into any of the usual diagnostic categories. This is the type of history one often obtains from patients with temporal lobe spikes, as has been described in detail in two previous papers by Ervin and Epstein.§ In fact, one of the patients in our series was written up in detail by Epstein and Ervin [8] (Patient M. G.). If one would emphasize in the history the episodic nature of her symptoms, as well as the clouding of sensorium, the diagnosis would be psychomotor epilepsy with a rather prolonged ictal response. If one would emphasize the schizoid and paranoid features in her personality, as well as the prolonged agitation and homicidal-suicidal behavior accompanied by visual and auditory hallucinations, the tendency would be to consider this person a catatonic schizophrenic. On the other hand, the impulsive behavior extending far back into childhood would suggest childhood behavioral disorders characteristically described as the impulsive hysterical acting out in adulthood. This type of diagnostic dilemma was typical of almost all the patients in this series who showed the psychotic response to activation with SAC.

The episodic impulsive behavior was most frequently an expression of rage, varying from childish temper tantrums, in which the patient would lie down on the floor, kick, and scream, through impulsive and sudden outbursts of physically abusive behavior toward those closest to him, to, rarely, the more organized acted-out dissocial behavior, such as stealing and forging checks. Quite often this rage was turned on the self, with bizarre suicidal attempts or self-mutilation. At other times, the episodic behavior was more typical of seizural states with loss of consciousness, but rarely typical grand mal attacks; more frequently there were diffuse automatic movements characteristic of psychomotor epilepsy. These episodic attacks were frequently accompanied by disorientation and amnesia, but not invariably so. The amnesia often seemed more a conscious malingering to deny responsibility for the hostile acts committed, as, for instance, was dramatically represented in one patient who was hospitalized because her behavior was accompanied by amnesia. Immediately after hospitalization, to gain her release, she proved the amnesia was a fabrication by relating in minute detail the events of the preceding 24 hours for which she had previously claimed complete amnesia. At times the episodic behavior was more typical of catatonic mutism, and at other times it was just episodic depersonalization or seductive and self-destructive acting out.

The behavior between the episodic outbursts would be characterized by poor interpersonal relationships and social adjustment, usually accompanied by narcissistic, self-centered preoccupation, irritability, paranoid trends, and lack of close emotional attachments.

Contrariwise, in many instances, those patients who had definite evidence of psychosis but whose symptoms were well structuralized, with organized delusions and adequate, if bizarre, control, and who were characterized previously by obsessive-compulsive rigid personalities, generally did not show electroencephalographic activation or marked behavioral changes under chloralose.

We seldom had the opportunity to run EEG records at the time of a spontaneous attack. In several instances when we did, the seizure was associated with spontaneous high-amplitude slow waves, similar to those induced by SAC. However, in the case here described, during the spontaneous attack there was no change in the scalp recordings from the base-line record, which showed a slight abnormality with 6 and 7½ per second generalized slow waves.

Comparison with Other Drugs

Fourteen of the subjects in this study had intravenous amobarbital sodium given slowly while they were interviewed: Five

§ References 7 and 8.

were given *d*-LSD-25; 3, mescaline; 5, pentylenetetrazol, and 2, intravenous alcohol. Although some of the patients demonstrated episodic behavior as an obvious release phenomenon (under the influence of alcohol, for instance), we did not find that the patients who showed psychotic behavior under SAC responded in a similar manner when given amobarbital sodium intravenously to the point of slurring of speech without inducing sleep. If anything, they tended to normalize under amobarbital sodium, whereas those patients who showed a release phenomenon, with more psychotic behavior, under amobarbital did not respond in a similar manner with SAC. The reactions of the patient described above will be reported in some detail, with any deviations in the response of the other patients mentioned.

March 29, 1955: Chloralose. During the baseline recording the patient was pleasant and friendly, cooperative, and oriented in all spheres. Forty minutes after the drug she was crying and depressed. At one hour she complained of numbness in her right hand and arm. She described an "odd feeling," similar to that when her attacks come on, which, on questioning, suggested depersonalization. At 70 minutes she was expressing diffuse rage and tearing up the bedclothes. She admitted concern about her children and her inability to take care of them. Eighty-five minutes after the drug she complained of shakiness and showed occasional myoclonic jerks in the arm. Ninety minutes after the drug she began hallucinating, with her children and husband appearing before her and admonishing her for being bad. She verbally responded to these hallucinations. At that time, though somewhat confused, she was still perfectly oriented. At 100 minutes she began screaming, "Where am I?" and now appeared disoriented, thinking that she was in a different town and different hospital, although, on repeated questioning, she remembered vaguely where she was. More depression was seen now and less rage. At this time she revealed some significant dynamic material which had been inferred from the clinical history, namely, that she was overwhelmed with the responsibility of raising her children, felt guilty that she had been abusive and tried to kill them, and admitted that she expected retribution from her mother, who would not allow her to grow up and be a mother in her own right; therefore, the children must belong to her mother and are really her father's children. She expressed guilt over these incestuous fantasies, as well as fear of retaliation from her mother. Often, during an acute attack, she discussed leaving the children with her mother and moving to a distant city to live with her father. Except for the hallucinations, which occurred in only three instances, this is a rather typical activation of psychotic behavior by SAC.

May 23, 1955: Pentylenetetrazol, 700 mg., injected slowly intravenously. Except for mild subjective sensations of anxiety, there were no changes in behavior. During the next 24 hours, she participated in all ward activities, went on passes with her husband, and had no difficulty in sleeping and no somatic complaints. Most of the other patients who received Metrazol had some somatic side-effects; otherwise, this response was a fairly typical one.

May 27: Chloralose repeated. Interestingly, at this time, the patient showed no hallucinations and no bizarre acting out of rage or marked fear and depression. She had the same feeling of depersonalization and showed more clouding of sensorium, with organic confusion and perseveration.

May 30: *d*-LSD-25, 100γ. Forty minutes after the drug was given, the patient complained of feeling tense and "paralyzed," stating that she couldn't talk, although there was no obvious impairment in her speech. At 45 minutes she became nauseated and complained of blurred vision. One hour after administration of the drug, eye pressure revealed red lights, "maybe Indians." At 90 minutes she stated that she had to get up and go home to her children; she was crying and struggling. There was some difficulty in remembering the doctor's name, as she seemed to be in a "trance-like state." When her attention was secured, she was oriented and in contact with her surroundings. Two hours after the drug was given, a blocking agent was administered, which modified the subsequent response. At one time, she briefly hallucinated her children, but there was no conceptual elaboration on the basis of dynamic material, as described under the first chloralose reaction.

June 1: Mescaline sulfate, 500 mg. I.V. The immediate response was a sensation of being cold. "My skin is burning." She also complained of difficulty in breathing; she vomited, and described sensations in her legs as if they were "drawing up." She expressed anger at the doctor, as well as her husband, but would laugh while talking about it. She did mathematical problems quickly and was oriented in all spheres. One and one-half hours later, she complained of aches and pains in her back and neck; she saw lights flashing, saying it was as if "you look sparkly." There were no marked emotional changes, nor did she hallucinate at this time. In comparison with SAC, LSD and mescaline seem to induce more somatic complaints,

less acting out, more perceptual distortions, but less conceptual ones.

June 3: Repeated chloralose plus amobarbital sodium, 7½ grains. At this time, the patient responded to the chloralose as she did in the first experiment, again becoming agitated, rageful, tearing up things, and hallucinating her children and husband, the children being frightened, and the husband admonishing for her rageful behavior. After amobarbital was given the patient quieted down, no longer expressed anger and resentment, but, rather, showed expiatory behavior: "Do you like me?" and "Nobody's going to kill me, are they?" She said she was no longer angry at her husband or the doctor, and stated that, although she occasionally saw her children, "they are now smiling." In several other instances when amobarbital sodium was given, after a psychotic reaction with chloralose, a similar type of response would ensue, wherein the psychotic material, particularly the frightening and rageful affect, was reduced.

June 6: Spontaneous attack. On the ward she was restless, paced the floor, was no longer cooperative, and refused her medicine, stating, "I feel one of my moods coming on, and I am going to tear up everything." She tried to run away from the hospital and expressed a desire never to see her doctors again. She threatened the personnel, threw about the belongings in her room, and by evening was depressed and crying. She began tearing up her clothes and had to be forceably restrained. Twelve hours after the start of the spontaneous seizure, she was quieter, less agitated, and expressing some guilty feelings about her previous behavior, which she remembered clearly. This illustrates that the episodic psychotic behavior was not always accompanied by amnesia.

Comment

There has been an increasing awareness among psychiatrists and neurologists of a borderline group of severe behavior disorders, variously diagnosed as psychomotor epilepsy, hysterical acting out, or schizophrenia. The diagnostic category in which these patients are placed depends not only on the orientation of the physician, that is, whether he is a neurologist, a psychoanalyst, or a psychiatrist, but also on the acuteness of onset, the duration of disturbed behavior, and the degree of sensorial changes and subsequent amnesia. Therapeutic trial, either on anticonvulsive medication or on the usual somatic therapies for schizophrenia, particularly EST and insulin, has not aided in the proper diagnostic categorization of these patients because of their poor response to all somatic therapies, although it has been our experience that they often show marked improvement with intensive psychotherapy. Base-line EEG's are usually normal or equivocal, and electroencephalograms are usually impossible to obtain during acute attacks, so that laboratory procedures offer little diagnostic clarification. The complicated conceptually organized patterns of behavior manifest during these spells, and often concomitantly expressed in dreams, usually reveal dynamically significant material, particularly expressions of rage and destructiveness toward Oedipal figures or sibling rivals, have reinforced the psychological importance of such episodic behavior, and perhaps oftentimes tended to minimize adequate neurologic and laboratory workups. As mentioned in the paper originally, many of our patients were selected for this study on the basis of being in this borderline group, although subsequently we made a conscious attempt to select them at random. To us it was not surprising, then, that many of the patients in this group, like the epileptic or focal neurologic patient, showed an activation of cerebral hypersynchrony under SAC. Without postulating a common etiologic relationship between epilepsy and these episodic psychotic states, we now believe that it can be demonstrated that both have this common potential for cerebral hypersynchrony. It seems to us that the historic observation of incompatibility between epilepsy and schizophrenia is best reformulated as follows: The massive cerebral discharges involving the motor areas and resulting in typical grand mal seizures do seem to protest against or alleviate the psychotic manifestations that otherwise might be present. However, we would like to suggest the idea that there may be a closer relationship mechanistically among these episodically disturbed patients, in categories now variously diagnosed as hysteria, psychomotor epilepsy, catatonic schizophrenia, episodic alcoholism,

and impulsive dissocial behavior, than there is with those patients in the same diagnostic category who show sustained, nonepisodic, disturbed behavior.

Interestingly, Karl Menninger,[12] in his revision of psychiatric nosology, based on modified psychoanalytic concepts, has come to similar conclusions, grouping together a number of episodic clinical syndromes under the heading of "Regulatory Devices of the Third Order: Episodic Discontrol." In describing this group, he states:

> The uncontrollable emergence of dangerous instinctual impulses is always something of a catastrophy. . . . Clinically and empirically we know these catastrophies in two forms; as continuous phenomena over a considerable period of time, and as a relatively brief episodic discontinuous phenomenon from which there is prompt recovery with a continued tendency for them to recur. It would seem that these episodic explosions serve to relieve enough tension to prevent the development of the continuous form.

Recent neurophysiologic studies have revealed that in both man and animals electrical stimulation of certain subcortical structures, particularly the septal and hippocampal-amygdaloid regions, can induce dramatic changes in behavior with or without changes in sensorium. In a recent article, French and associates[9] demonstrate that it is precisely these subcortical areas which would show seizural activity when the cortex is stimulated with parameters of currents that would elicit local "seizural-type" after-discharges. If there was subsequent spread of this local response, it would occur most frequently in the septal-amygdaloid region. Thus, it is not hard to conceive that the spontaneously induced hypersynchronous activity might result in rather complicated behavioral changes, and that these do not necessarily have to be accompanied by loss or impairment of consciousness or dramatic clouding of sensorium. We must admit, however, that our present study thus far has not revealed any precise correlation of central nervous system, electrophysiologic activity, and behavior. In view of the crudeness of our clinical technique, particularly the use of scalp recordings of the electrophysiologic activity of the cortex, this is not surprising. However, the present data do give impetus to more intensive study of the electroencephalogram in psychotic patients using activators, and also suggest renewed efforts in developing the "anticonvulsant" group of drugs, which may hold some hope for at least a pharmacological adjunct to our present psychotherapeutic efforts in those patients with episodic behavior disorders.

Summary

Electroencephalographic and behavioral activation with chloralose and scopolamine was done on a group of volunteers, neurologic patients, and psychiatric inpatients. There was a low incidence of EEG activation in volunteers without psychologic disorders or neurologic complications. In the neurologic patients with evidence of focal central nervous system lesions, there was almost always EEG activation compatible with the diagnosis, even though previous EEG's had been normal or equivocal. In patients with a good history of epilepsy but normal or equivocal EEG's, there was again, almost inevitably, electroencephalographic activation compatible with the clinical diagnosis.

Surprisingly, 48 of 65 psychiatric inpatients also showed electroencephalographic activation, with the appearance of high-amplitude paroxysmal delta-theta activity and/or focal or generalized spikes.

Of the 48 activated psychotic patients, 24 demonstrated an exacerbation of psychotic behavior while under the influence of chloralose and scopolamine, as compared with only 2 of the 45 volunteers or neurologic patients who showed electroencephalographic activation. The psychotic behavior was usually characterized by rageful acting out, depersonalization, and confusion, and, rarely, by hallucinations and delusions. The reaction to the drug was usually similar to the spontaneous psychotic behavior previously shown by the patient. Activation of the psychosis by scopolamine-α-chloralose

seemed to occur predominantly in a group of patients who had shown clinically the impulsive acting out demonstrated under the drug.

REFERENCES

1. Adrian, E. D.: Afferent Discharges to Cerebral Cortex from Peripheral Sense Organs, J. Physiol. 100:159-191 (Sept. 8) 1941.

2. Adrian, E. D., and Moruzzi, G.: Impulses in Pyramidal Tract, J. Physiol. 97:153-199 (Dec. 14) 1939.

3. Bercel, N. A.: Experience with Combination of Scopolamine and Alpha-Chloralose (S. A. C.) in Activating Normal EEG of Epileptics, Electroencephalog. & Clin. Neurophysiol. 5:297-304 (May) 1953.

4. Baruk, H.: Action physiologique expérimentale et clinique du scopochloralose: Scopochloralose et bulbocapnine; application à quelques problèmes de la catatonie expérimentale, Ann. med.-psychol. 94:702-712 (Nov.) 1936.

5. Council for International Organizations of Medical Sciences: Brain Mechanisms and Consciousness; a Symposium, edited for the Council by J. F. Delafresnaye, Springfield, Ill., Charles C Thomas, Publisher; London, Blackwell Scientific Publications, 1954.

6. Ellingson, R. J.: Brain Waves and Problems of Psychology, Psychol. Bull. 53:1-34 (Jan.) 1956.

7. Ervin, F.; Epstein, A., and King, H. E.: Behavior of Epileptic and Nonepileptic Patients with "Temporal Spikes," A. M. A. Arch. Neurol. & Psychiat. 74:488-497 (Nov.) 1955.

8. Epstein, A., and Ervin, F.: Psychodynamic Significance of Seizure Content in Psychomotor Epilepsy, Psychosom. Med. 18:43-55 (Jan.-Feb.) 1956.

9. French, J. D.; Gernandt, B. E., and Livingston, R. B.: Regional Differences in Seizure Susceptibility in Monkey Cortex, A. M. A. Arch. Neurol. & Psychiat. 75:260-274 (March) 1956.

10. Hill, Denis: EEG in Episodic Psychotic and Psychopathic Behavior, Electroencephalog. & Clin. Neurophysiol. 4:419-442 (Nov.) 1952.

11. Monroe, R. R.; Heath, R. G.; Miller, W., and Fontana, C.: EEG Activation with Chloralosane, Electroencephalog. & Clin. Neurophysiol. 8:279-287 (May) 1956.

12. Menninger, K.: Regulatory Devices of the Ego Under Major Stress, Internat. J. Psycho-Analysis, 35:412-420, 1954.

13. Rosenblueth, A., and Cannon, W. B.: Cortical Responses to Electric Stimulation, Am. J. Physiol. 135:690-741 (Feb.) 1942.

14. Verdeaux, G.; Verdeaux, J., and Marty, R.: L'Activation des électroencéphalogrammes par le chloralose, Electroencephalog. & Clin. Neurophysiol. 6:19-28 (Feb.) 1954.

Adrenal Cortical Function in Anxious Human Subjects

Plasma Level and Urinary Excretion of Hydrocortisone

HAROLD PERSKY, Ph.D.
ROY R. GRINKER, M.D.
DAVID A. HAMBURG, M.D.
MELVIN A. SABSHIN, M.D.
SHELDON J. KORCHIN, Ph.D.
HAROLD BASOWITZ, Ph.D.
and
JACQUES A. CHEVALIER, Ph.D., Chicago

The hormones of the adrenal cortex contribute significantly to processes of adjustment to noxious stimuli,[1] although much disagreement exists as to their mode of action.* Physical stresses, such as trauma or surgery, considerably increase the blood level of the adrenocortical hormone hydrocortisone,[4] as well as the excretion of several of its metabolites, tetrahydrocortisone and tetrahydrohydrocortisone.† Psychological stresses imposed in various ways also raise the blood and urine levels of these hydroxycorticoids.‡

From the available data, it seems justified to conclude that many kinds of stress increase the secretory activity of the adrenal cortex. However, it is possible that increased blood levels of hydrocortisone may result from diminished hepatic disposal and that increased urinary excretion is responsible for the larger quantities of urinary hydroxycorticoids. Direct proof of an increased secretory rate by the adrenal cortex could only be obtained through the determination of the adrenal vein minute-output of hydrocortisone under basal and stress conditions. Since this is not feasible in intact humans, it becomes necessary to rely on indirect evidence elicited by a total metabolic study of hydrocortisone during basal conditions and following the induction of specific stresses.

We have been engaged for some years in a program of research into the psychosomatic organization of anxiety, the theoretical assumptions of which have been reported previously.[10] In this paper we present a comparison of the quantities of hydrocortisone in the plasma and the amounts of tetrahydrocortisone and tetrahydrohydrocortisone excreted in the urine in anxious and control subjects under experimental conditions. Other findings concerning the production and disposal of hydrocortisone will be presented in subsequent publications.

Received for publication July 2, 1956.

From the Institute for Psychosomatic and Psychiatric Research and Training, Michael Reese Hospital.

This study was supported in part by the U. S. Army under Contract No. DA-49-007-MD-469 through the Medical Research and Development Board, Office of the Surgeon General, Department of the Army, and by the State of Illinois Mental Health Fund.

* References 2, 3.

† References 5, 6.

‡ References 7-9.

Subjects, Experimental Design, and Methods

The experimental subjects (E1) consisted of a group of 21 patients, 12 men and 9 women, on a psychiatric service of a general hospital. Their ages ranged from 20 to 58 years, with a mean of 38.7 years. All patients had in common some degree of anxiety or anxiety proneness. The criterion for anxiety was the patient's experience of a feeling of dread and foreboding—as if something dangerous were about to happen. The presence or absence of anxiety was determined by two psychiatric observers who were engaged in the anxiety research program of the Institute. If anxiety was present, they estimated its intensity on a seven-point scale. This estimate was based

on the patient's verbal report of his emotional experience at the time, augmented by such nonverbal signs as facial expression and motor and autonomic activity. Thus the evidence for these ratings came from two sources: (1) observation of the entire experiment by two psychiatrists through a one-way-vision screen, and (2) psychiatric interviews, before and after the experimental stress, designed specifically to elicit information about the patient's experience at each point in the experiment. The final ratings represent a consensus estimate of the independent ratings made by the two observers. The patient group was in good health, as judged by physical examination, and were not receiving interfering medication.

On each of four successive days, three blood samples were drawn from every member of Group E1: 9:00 a.m., 10:30 a.m. and 2:30 p.m. These samples will be referred to as pre-, post-, and extra-post-values, respectively. The pre-sample of the first day ("base day") was drawn on the patient's nursing unit, but all of the other pre- and post-samples were drawn in the experimental room. The extra-post-samples were drawn on the nursing unit. On the "base day" the subjects were brought to the experimental room in order to familiarize them with the room and the apparatus required for various physiological and psychological procedures carried out as part of the larger study. On each of the last three days (Day 1, Day 2, Day 3), a stressful interview, lasting about 30 minutes, was interposed between the pre- and post-samples of blood. The interview attempted to evoke overt anxiety in the patient by discussing specific psychological problems known to be disturbing to the patient. Three of the twenty-one subjects withdrew from the experiment because the procedure was too disturbing emotionally.

Complete 24-hour urine outputs were collected on each of the four testing days for every subject. The urine was collected in two portions: one for the period from 8:30 a.m. to 2:30 p.m., and the other from 2:30 p.m. to 8:30 a.m. of the following day. The first six-hour quantity of each day bracketed the total experimental testing period.

The base day was initially included in the design for Group E1 to familiarize the subjects with the experimental room, apparatus, and procedures. It was assumed that the plasma hydrocortisone level would follow a normal diurnal course on this day, since no stress interviewed was included. However, it was found that the plasma hydrocortisone level increased even more than on any of the experimental days, a finding which might be due to the strangeness of the preparations and procedures. Consequently, a second group, of eight subjects (E2), from the same patient population, who resembled the experimental subjects (E1) in respect to anxiety, was also tested under considerably less disturbing conditions. These subjects remained on their own nursing units instead of being taken to the laboratory; only two blood samples were drawn from each subject, and no other test procedures were carried out. The blood samples were drawn at the pre- and post- times of the Group E1 subjects. No stress interview was conducted with these Group E2 subjects. Thus the conditions for testing this group represented a better "basal state" for anxious patients than did those on the "base day" for Group E1.

In order to compare the anxious subjects with normal subjects, two groups of controls were employed. The first group consisted of 16 doctors, nurses, and technicians (C1), ranging in age from 24 to 45 years, with a mean of 32.2 years. Seven of these subjects were men and nine were women. The Group C1 subjects were not hospitalized and were in good physical health. On each of five separate occasions, spaced a week apart, a blood sample was drawn at 9:00 a.m. from every member of this group in a laboratory room similar to the experimental room employed for Group E1 subjects. On the first of these five occasions, a 24-hour urine sample was collected. The purpose of the first-day blood and urine sampling was to enable comparisons to be made between anxious subjects and normal controls with respect to their "basal" state. The repetitive blood collections from the Group C1 subjects were made in order to determine whether any trend in plasma hydrocortisone level occurred over a period of time somewhat greater than the duration of the Group E1 experiment. No stress interview was conducted with the control subjects.

The second group of control subjects consisted of 24 college students (C2), 20 male and 4 female, with a mean age of 21.9 years. Half (12) of the Group C2 subjects were found to be less anxious than either patient group in a diagnostic psychiatric interview three days prior to blood sampling. All of the students were carefully examined and found to be in good physical health. A blood sample was drawn from every student at 9:00 a.m. on each of three successive days. All samples were drawn in the same laboratory setting as that employed for subjects of Group C1. No stress interview was conducted with this group. The students served two purposes: (1) Being unfamiliar with the laboratory setting, they were expected to react to the novelty of a new situation and to have anticipatory anxiety about the strange laboratory setting, and (2) they supplied information about the trend of plasma hydrocortisone level over a period of days comparable to the time span of the Group E1 experiment.

All blood samples were centrifuged immediately,

and the plasma content of hydrocortisone was determined by the method of Nelson and Samuels.§ Urine samples were kept in the refrigerator without preservation until the entire 24-hour collection was completed. The hydroxycorticoid content was determined according to the method of Reddy, Jenkins, and Thorn[13] as modified by Brown and his co-workers.[14] As a check on the completeness of the urine collection, the creatinine content was determined for every sample.[15]

Results

Plasma Hydrocortisone Level

The concentration of hydrocortisone in the plasma constitutes a balance between the secretory rate of the subject's adrenal cortex and the rate of hormone destruction and excretion by the peripheral tissues and kidneys. The 9:00 a.m. plasma level of hydrocortisone on the "base day" was about 60% greater in the anxious subjects (E1) than in either of the control groups (Table 1). This difference is statistically significant at better than the 1% level of confidence. The normal values obtained from our control groups agree closely with the reported values for physically healthy subjects.‖ The experimental subjects' levels ranged from 8.7γ to 34.5γ per 100 cc., while the levels for the normal controls of Group C1 ranged from 2.4γ to 21.6γ per 100 cc. Only one subject in the control group had a plasma hydrocortisone level greater than the mean of the anxious-patient group. The range for Group C2 subjects extended from 4.7γ to 25.6γ per 100 cc., and here, again, only two members were above the mean of the anxious-patient group (E1). The variability of the 9:00 a.m. hydrocortisone level is not significantly greater in the experimental than in the normal groups on the pre-stimulus day. The difference in level between the anxious subjects and the normal controls indicates that the balance between production and destruction in the absence of experimentally imposed stress is pegged at a considerably higher level in the anxious subjects.

TABLE 1.—*"Base-Day" Plasma Hydrocortisone Pre-Levels of Anxious and Normal Subjects*

Group	No. of Subjects	Plasma Hydrocortisone Level, γ/100 Cc.		t*	P
		Mean	Standard Deviation		
Experimental (E_1)	18†	19.5	6.6		
Normal (C_1)	16	12.1	5.9	3.58	<0.005
Normal (C_2)	24	12.7	5.3	3.70	<0.001

* Between E_1 and the other groups.
† In this and in the succeeding Tables, the number of subjects in each group may vary slightly because of an occasional loss of a sample.

The mean hydrocortisone pre-level (9:00 a.m.) of the anxious patients (Group E1) did not vary greatly over the four days of testing, as shown by an analysis of variance (Table 2). The normal controls also maintained a constant 9:00 a.m. level of hydrocortisone for a period ranging from three

§ References 11, 12.
‖ References 14, 16-19.

TABLE 2.—*Repetitive Plasma Hydrocortisone Pre-Levels of Anxious and Normal Subjects*

Group	No. of Subjects	Occasion Interval	Plasma Hydrocortisone Level, γ/100 Cc.*					F	P
			Occasion 1	Occasion 2	Occasion 3	Occasion 4	Occasion 5		
Experimental (E_1)	18	Daily	19.5±4.7	20.9±6.1	18.6±6.2	18.1±6.8		1.46	Not sig.
Normal (C_1)	16	Weekly	11.9±5.8	12.5±4.1	12.6±4.0	12.0±4.3	11.7±3.3	0.09	Not sig.
Normal (C_2)	12†	Daily	13.5±6.2	12.3±6.3	10.8±3.6			0.78	Not sig.

* Mean±standard deviation.
† Only 12 of the 24 subjects are included, since the between-day treatments of these 12 are identical.

days, for Group C2, to four weeks, for Group C1. The relative constancy of level within each group suggests that the difference between the anxious group and the control group is biologically, as well as statistically, different.

Effect of Stress Interview on Plasma Hydrocortisone Level

Although the plasma hydrocortisone levels of anxious patients are considerably higher than those of normal subjects, an increase in anxiety might be expected to raise this hormonal level even more. In order to understand the changes in level that occurred and to appreciate the statistical techniques employed to compare the change in level on the stress days with the change in level on the "base day," some information concerning the diurnal course of the plasma hydrocortisone level is appropriate. Bliss and his associates [16] have demonstrated that in normal subjects the blood hydrocortisone level changes during the day; it achieves a peak in the morning and then falls until late afternoon, after which it remains relatively steady, returning to the original high level by the following morning. The sharpest rate of fall occurs between 8:00 a.m. and 12:00 noon, the period during which the bulk of our procedures occurred. Anxious patients also manifest this diurnal pattern, as can be seen from the data of Group E2 in Table 3. Over comparable periods of the day, the decrease in plasma hydrocortisone level of Group E2 subjects is about the same as that of normal controls. The change of level in Group E2 is therefore presumed to represent the diurnal decrease in plasma hydrocortisone level that would occur in anxious, hospitalized patients not subjected to any intended stress. When this diurnal decrease is subtracted from the change in hydrocortisone level for Group E1, the difference may be taken to represent the effect of the imposed stress.

On any given experimental stress day, the change in level (post- minus pre-value) for Group E1 did not differ significantly from that for the anxious "control" subjects of Group E2 (Table 3). The greatest relative response occurred on Day 2, but this failed to achieve significance. Specific subjects on each of the experimental days did manifest large increments in plasma hydrocortisone; indeed, the two highest levels achieved, 62.5γ and 42.3γ per 100 cc., reflecting increases of 49.8γ and 23.7γ per 100 cc., respectively (57.4γ and 31.3γ per 100 cc. when diurnal fall is subtracted), occurred in the subjects who were unable to continue with the total experiment because of the intensity of disturbance aroused in them by the stress interview. On each of the experimental days, the anxious subjects did not exceed their own "base-day" change from pre- to post-level (Table 3). Actually, the "base-day" change in level was signifi-

TABLE 3.—*Change in Plasma Hydrocortisone Level Following a Stress Interview*

Group	No. of Subjects	Occasion	Plasma Hydrocortisone Level, γ/100 Cc.*			t†	t‡	Post-Minus Pre-Increase Due to Stress§ γ/100 Cc.
			Pre-	Post-	Post- Minus Pre-			
Experimental (E_2)	8	"Base day"	21.7±9.5	14.2±7.0	−7.56± 6.81			
Experimental (E_1)	18	"Base day"	19.5±6.6	19.6±6.8	0.11± 7.52	2.46‖		7.67
Experimental (E_1)	18	Day 1	21.7±7.3	15.6±5.1	−6.14± 7.12	0.47	2.28‖	1.42
		Day 2	18.1±6.6	14.8±7.3	−3.29±10.00	1.60	1.32	4.27
		Day 3	19.3±5.9	13.3±6.7	−5.99± 8.20	0.48	2.64¶	1.57

* Mean±standard deviation.
† Between E_2 and E_1 on each occasion.
‡ Between E_1 on "base day" and E_1 on each of the three experimental days.
§ Post- minus pre-value after the diurnal decrease has been removed.
‖ Significant at better than the 5% level of confidence.
¶ Significant at better than the 2% level of confidence.

cantly greater than the change on Day 1 or Day 3.

The failure to detect a significant change in plasma hydrocortisone in response to the stress imposed on Group E1 may be due to an inappropriate time of sampling in relation to the time of the stress interview. It was with this possibility in mind that an additional post-stress sample (extra-post-sample) was built into the experimental design. The extra-post-sample was drawn four hours after the post-sample and an average of four and one-half hours after the stress interview. Although a few subjects did respond with a prolonged elevation or a delayed rise in plasma hydrocortisone, the group as a whole did not manifest a significant increase in level during the pre- to extra-post-period. Actually, the mean extra-post-value was even lower than the post-value on every experimental day. This is the expected diurnal course of plasma hydrocortisone. However, when the change in anxiety resulting from the stress interview was rank-ordered for each subject according to intensity (high, medium, low), the mean increase in hydrocortisone level for the group with respect to extent of change in anxiety was significantly different, as shown by an analysis of variance (Tables 4 and 5). The increase in hydrocortisone level after diurnal change was subtracted was not very large (5.0γ per 100 cc.) on the day on which the subjects experienced their greatest change in anxiety. A slight decrease of only 0.8γ per 100 cc. occurred on the occasions when anxiety changed the least. The change in hydrocortisone level is related to the change in anxiety in a linear fashion. This is true not only for the group as a whole but also for each individual. The post-level achieved on the day of greatest increase in anxiety, corrected for diurnal fall, is 28% greater than the pre-level for the anxious group and 90% greater than that of the normal control group, C1. The moderate rise in plasma level of the anxious subjects parallels the moderate increase of anxiety resulting from the stimulus interview.

On the "base day" of Group E1, the change in level was significantly greater than the change in level for Group E2

TABLE 4.—*Effect of an Increase in Anxiety Rating on Plasma Hydrocortisone Level*

Occasion	Plasma Hydrocortisone Level, γ/100 Cc.*			
	Pre-	Post-	Post- Minus Pre-	Post- Minus Pre- Increase Due to Stress
Day of maximum anxiety increase for each subject	17.88±6.04	15.31±6.99	−2.57±8.28	4.99
Day of median anxiety increase for each subject	18.71±6.10	15.43±6.02	−3.28±5.44	4.28
Day of minimum anxiety increase for each subject	21.96±7.48	13.61±5.52	−8.37±8.45	−0.81

* Mean±standard deviation, for 17 subjects.

TABLE 5.—*Analysis of Variance of Changes in Plasma Hydrocortisone Level (Post- Minus Pre-Values) for Various Degrees of Change in Anxiety Ratings*

Source of Variation	*df*	Mean Square	*F*	*P*
Between subjects	16	77.11	1.67	Not sig.
Between levels of change in anxiety ratings	2	170.25	3.69	<0.05
Liner	(1)	285.94	6.19	<0.02
Quadratic	(1)	54.56	1.18	Not sig.
Error	32	46.18		
Total	50			

(Table 3). The extent of disturbance produced by the "base-day" experience of Group E1 was greater than on any of the stress days, and also caused a higher mean extra-post-level in the afternoon. Thus Group E1 maintained a higher plasma hydrocortisone level over a longer period of time on the "base day" than on any experimental day.

Urinary Hydroxycorticoid Excretion

After its release into the circulation, hydrocortisone is extensively modified by the liver,¶ and the metabolic products are excreted (almost in entirety) by the kidney.[22] The metabolism of the hormone involves both ring and side-chain reduction and oxidation, as well as conjugation. No quantitative balance studies have been made to date for the relationship of hydrocortisone and its inert end-products. However, three major types of metabolic products have been identified and measured roughly: the dihydroxyacetone side-chain compounds, consisting chiefly of tetrahydrocortisone and tetrahydrohydrocortisone,[5] the glycerol side-chain compounds of the "cortol" (pregnane-3α, 11β, 17α, 20α, 21-pentol) and "cortolone" (3α, 17α, 20α, 21-tetrahydroxypregnane-11-one) type [23] and the 17-ketosteroids.# This rough division has been achieved by the use of steroid classificatory reagents, such as phenylhydrazine, periodate, and dinitrobenzene. In the present study only one moiety of the hydrocortisone metabolites was assessed quantitatively: the phenylhydrazine-reacting substances present in an acid-butanol extract of urine (Porter-Silber reaction). The latter substances are almost exclusively tetrahydrocortisone and tetrahydrohydrocortisone, with small amounts of hydrocortisone and cortisone. More than 95% of the chromogenic material is conjugated as the glucuronide or sulfate. Since this fraction is about one-fifth of the daily hydrocortisone production by the normal adrenal gland,* one must be extremely cautious in drawing conclusions from changes in this measure, inasmuch as any differences found may reflect shifts in the metabolic pattern rather than alterations in adrenocortical function.

The 24-hour excretion of phenylhydrazine-reacting substances (hydroxycorticoids) on the base day in anxious subjects (Group E1) is 70% greater than in normal controls (C1) (Table 6). The value for our control group is identical with those reported for normal subjects by other investigators.† The increased urinary output of steroid by the anxious patients was not due to increased urinary output, since the volume in the two groups did not differ significantly; the normals actually put out a slightly larger volume

¶ References 20, 21.

Munson, P. L.: Laidlow, J. C.; Goetz, F. G.; Jenkins, D., and Thorn, G. W.: Effect of Corticosteroids on 17-Ketosteroids and Androgen Excretion, unpublished data, cited by Thorn and associates.[24]

* References 14, 25.

† References 13, 14.

TABLE 6.—*"Base-Day" Urinary Excretion of Hydroxycorticoids by Anxious and Normal Subjects*

Group	No. of Subjects	Urine Hydroxycorticoids, Mg.*		
		A.M.†	P.M.‡	24 Hr.
Experimental (E_1)	16§	3.28±2.30	4.77±3.53	8.04±5.20
Control (C_1)	16	2.25±1.39	2.52±1.50	4.77±2.38
	t	1.52	2.35	2.29
	P	Not sig.	<0.05	<0.05

* Mean±standard deviation.
† Period from 8:30 a.m. to 2:30 p.m. (6 hours).
‡ Period from 2:30 p.m. to 8:30 a.m. next day (18 hours).
§ Complete data for only 16 of the 18 subjects.

(1525±873 cc. *vs.* 1418±909 cc.; $t=0.34$; P not significant). During the period from 8:30 a.m. to 2:30 p.m. on the base day, the anxious subjects excreted more hydroxycorticoids, but this difference was short of significance; only in the afternoon and evening did a clear differentiation between the anxious and the normal subjects with respect to hydroxycorticoid excretion occur. This increased excretion is related to the higher levels of hydrocortisone in the plasma of the anxious subjects for the three sampling times as compared with the normal controls.

The excretion of hydroxycorticoids in anxious subjects ranged from 0.00 to 15.70 mg. on the "base day," while the normal controls (C1) ranged from 0.30 to 8.86 mg., with only one normal value above the mean of the anxious group. The anxious group was considerably more variable than the controls with respect to the quantity of hydroxycorticoids excreted on the "base day." The difference exceeded the 0.01 level of significance, as shown by the F-test.[26]

Since the plasma level of hydrocortisone and the urinary output of hydroxycorticoids of anxious subjects are increased to about the same extent (60% to 70%) over those for normals, it seems reasonable to conclude that the adrenal cortex in anxious patients is "set" to secrete hydrocortisone at an increased rate.

Effect of the Stress Interview on Urinary Hydroxycorticoid Excretion

It was anticipated that the urinary output of hydroxycorticoids would be increased following the stress interview. However, as with the plasma hydrocortisone level, no significant increase in urinary output was noted on any experimental day (Table 7). Specific subjects did respond with enormous increases in hydroxycorticoids, amounting to as much as 28.0 mg. per day. Because of the wide range of responses, the group variability was greater on every experimental day than on the "base day," with Day 3 achieving significance ($\sigma^2=60.00$ *vs.* $\sigma^2=24.24$; $F=2.47$; $P<0.05$) and Day 1 just short of significance.

TABLE 7.—*Change in Urinary Hydroxycorticoid Excretion in Eighteen Anxious Patients in Group E1 Following a Stress Interview*

Occasion	Urine Hydroxycorticoid Excretion, Mg./Day*	Comparison of Level		Comparison of Variance	
		t†	P	F	P
Base day	8.20±4.92				
Day 1	8.23±7.12	0.33	Not sig.	2.09	Not sig.
Day 2	6.20±5.54	1.33	Not sig.	1.27	Not sig.
Day 3	7.92±7.74	0.03	Not sig.	2.47	<0.05

* Mean±standard deviation.
† Between base day and each of the experimental days, a valu of 2.12 is necessary for the 5% level of significance.

No difference in hydroxycorticoid output occurred between occasions representing the extremes in anxiety arousal. This is distinctly different from the plasma hydrocortisone response when similarly analyzed. While no explanation is available to account for this difference between the urine and the plasma results, it may be that the change in plasma bears a direct relationship to the stimulation of the adrenal gland under the applied stress, whereas the urinary output reflects a variety of secondary effects of the stress, such as alteration in hepatic function. Since these influences may be operating in an antagonistic fashion, a clear differentiation between days with high and low changes in anxiety by means of the urinary hydroxycorticoid output may be impossible.

Comment

The anxious patient has been shown to maintain a considerably elevated blood hydrocortisone level and to excrete more hydroxycorticoids than less anxious controls.

In these respects he resembles the psychologically disturbed subjects of Board and his colleagues,[7] Elmadjian,[8] and Hetzel and his co-workers.[9] Furthermore, he responded to the application of a psychological stress of moderate intensity and short duration with a small rise in blood hydrocortisone level (after correcting for diurnal variation) but not in urinary hydroxycorticoid excretion. Relatively less disturbed subjects manifest an increase in urinary hydroxycorticoid output following a roughly similar stimulus,[9] while the output of normal men under the considerably greater stress of prolonged combat resemble our patient group by remaining unchanged.[8]

It is difficult to explain the elevated blood and urine steroid levels of the anxious subject in any fashion other than by assuming that his adrenal cortex has been stimulated to produce greater amounts of its major steroidal product.‡ While not satisfying the severest criteria, the combination of elevated plasma hydrocortisone and urinary tetrahydrocortisone levels has been accepted by other investigators as constituting presumptive evidence for increased adrenocortical secretion.[3] Alternative hypotheses might be acceptable if only the blood level or urinary excretion were increased; but with both these indices increased, no other explanation seems likely. That various biological events, in addition to an increase in adrenocortical activity, may occur which could further differentiate the anxious patient's hydrocortisone metabolism from others is a distinct possibility which cannot be dismissed without further investigation. It should be recalled, for example, that the conjugation of benzoic acid with aminoacetic acid to form hippuric acid is considerably enhanced in severely anxious subjects.[29]

The likelihood that the elevated plasma and urinary levels of hydroxycorticoids represent only disgorgement by the adrenal of stored hormone rather than continuous synthesis is slight in view of the fact that over several days of careful examination the same high levels were maintained. Furthermore, in at least some subjects the quantities of hydroxycorticoids excreted were equivalent to the estimated amounts produced daily by the gland.[25] The acceptance of the hypothesis of increased adrenocortical synthesis need not be based on indirect evidence alone. Direct techniques are presently available for the estimation of adrenocortical capacity § which can be applied in future studies.

What is the mechanism of adrenocortical activation in psychological stress? Hetzel and his associates[9] accept the view that adrenocortical activation occurs in response to increased catabolic processes occurring in the psychologically stressed as well as in the physically stressed organism, evidenced by increased nitrogen excretion and oxygen consumption. However, in a previous study of severe chronically anxious patients[29] it was found that the subjects maintained nitrogen balance while on a normal protein intake and had a normal basal metabolic rate throughout a testing period of four days. It seems more reasonable to assume that psychological stresses activate the adrenal cortex through the functions of the hypothalamic-pituitary system rather than by an indirect peripheral pathway.

Although the adrenal cortex appears to be hyperfunctional in chronically anxious men, the imposition of an additional anxiety-evoking stress did not elicit a large increase in their blood and/or urine hormone levels. The reason for this relative lack of response cannot be insufficiency of the function of the gland, since these subjects responded to intravenous corticotropin (ACTH) with large increments in blood and urine hormone content.¶ It is probably not due to pituitary insufficiency, since Sayers and his co-workers have shown that the pituitary has a large capacity to meet emergency demands for ACTH.# Two other explanations, not as fully explored, remain: (1) a failure of

‡ References 27, 28.

§ References 30, 30a.

¶ Persky, H.: Adrenal Cortical Function in Anxious Human Subjects: Production of Hydrocortisone, in preparation.

References 31, 32.

the central nervous system "triggering" mechanism for ACTH release to increase its stimulating activity in response to acute stress, or (2) an increase in utilization of adrenocortical hormone following acute stress, resulting in hormone levels in the blood and urine not differing from the pre-stress state. Neither possibility has been examined extensively in anxious subjects. Increased hormone utilization is known to occur after a variety of physical stresses,[31] and the sequence of events leading from the central nervous system to the discharge of ACTH by the pituitary remains to be explored.

The stress stimulus which we imposed on our anxious human patients could not ethically be too traumatic, so that the intensity of the elicited emotional responses was not great; nor did it persist for an extended period of time. It would be expected that the effect of the stress interview on adrenocortical hormone production would be slight. However, when over a period of days there was an increasing intensity of emotional arousal, there was a concomitant increase in the level of hydrocortisone in the plasma.

Summary

Plasma hydrocortisone level and urinary hydroxycorticoid excretion were 60% and 70% greater, respectively, in anxious subjects on a "base day" than in normal controls. The elevated blood and urine levels were maintained in the anxious subjects over a four-day testing period. When a stress interview was administered to every anxious subject on each of the last three days, it failed to increase significantly either the blood or the urine hormone levels in the group as a whole. When the stress days were segregated into high, medium, and low days for each subject, the change in plasma hydrocortisone level was significantly greater on the day of greatest increase in anxiety than on the day of least change in anxiety. The elevated plasma and urine hormone levels in the anxious subjects are taken as evidence that the adrenal cortex is secreting at a higher rate than in normal controls.

Miss Betty Lou Day, Mrs. Stiscie Cutler, and Mr. John Cowen assisted with the chemical determinations and did some of the statistical computation, and Dr. Helen Heath was responsible for a considerable part of the conception and execution of the statistical analyses.

REFERENCES

1. Selye, H.: The Physiology and Pathology of Exposure to Stress, Montreal, Acta, Inc., 1950.

2. Ingle, D. J.: The Role of the Adrenal Cortex in Homeostasis, J. Endocrinol. 8:23, 1952.

3. Engle, F. L.: General Concepts of Adrenocortical Function in Relation to the Response to Stress, Psychosom. Med. 15:565, 1953.

4. Sandberg, A. A.; Eik-Nes, K.; Samuels, L. T., and Tyler, F. H.: The Effects of Surgery on the Blood Levels and Metabolism of 17-Hydroxycorticosteroids in Man, J. Clin. Invest. 33:1509, 1954.

5. Cope, C. L., and Hurlock, B.: Some Aspects of Adrenal Cortical Metabolism, Clin. Sc. 13:69, 1954.

6. Birke, G.; Franksson, C., and Plantin, L. O.: The Excretion Pattern of 17-Ketosteroids and Corticosteroids in Surgical Stress, Acta endocrinol. 18:201, 1955.

7. Board, F.; Persky, H., and Hamburg, D. A.: Psychological Stress and Endocrine Functions: Blood Levels of Adrenocortical and Thyroid Hormones in Acutely Disturbed Patients, Psychosom. Med. 18:324, 1956.

8. Elmadjian, F.: Adrenocortical Function of Combat Infantrymen in Korea, Ciba Foundation Colloquia in Endocrinology, 1955, Vol. 8, p. 627.

9. Hetzel, B. S.; Schottstaedt, W. W.; Grace, W. J., and Wolff, H. G.: Changes in Urinary 17-Hydroxycorticosteroid Excretion During Stressful Life Experiences in Man, J. Clin. Endocrinol. 15:1057, 1955.

10. Grinker, R. R.; Korchin, S. J.; Basowitz, H.; Hamburg, D. A.; Sabshin, M. A.; Persky, H.; Chevalier, J. A., and Board, F. A.: A Theoretical and Experimental Approach to Problems of Anxiety, A. M. A. Arch. Neurol. & Psychiat. 76:420, 1956.

11. Nelson, D. H., and Samuels, L. T.: A Method for the Determination of 17-Hydroxycorticosteroids in Blood: 17-Hydroxycorticosterone in the Peripheral Circulation, J. Clin. Endocrinol. 12:519, 1952.

12. Eik-Nes, K.; Nelson, D. H., and Samuels, L. T.: Determination of 17, 21-Hydroxycorticosteroids in Plasma, J. Clin. Endocrinol. 13:1280, 1953.

13. Reddy, W. J.; Jenkins, D., and Thorn, G. W.: Estimation of 17-Hydroxycorticoids in Urine, Metabolism 1:511, 1952.

14. Brown, H.; Willardson, D. G.; Samuels,

L. T., and Tyler, F. H.: 17-Hydroxycorticosteroid Metabolism in Liver Disease, J. Clin. Invest. 33:1524, 1954.

15. Folin, O., and Wu, H.: A System of Blood Analysis, J. Biol. Chem. 38:81, 1919.

16. Bliss, E. L.; Sandberg, A. A.; Nelson, D. H., and Eik-Nes, K.: The Normal Levels of 17-Hydroxycorticosteroids in the Peripheral Blood of Man, J. Clin. Invest. 32:818, 1953.

17. Silber, R. H., and Porter, C. C.: The Determination of 17, 21-Dihydroxy-20-Ketosteroids in Urine and Plasma, J. Biol. Chem. 210:923, 1954.

18. Robinson, H. J.; Bernhard, W. G.; Grubin, H.; Wanner, H.; Sewekow, G. W., and Silber, R. H.: 17, 21-Dihydroxy-20-Ketosteroids in Plasma During and After Pregnancy, J. Clin. Endocrinol. 15:317, 1955.

19. Klein, R.; Papadatos, C.; Fortunato, J., and Byers, C.: Acid-Hydrolyzable Corticoids of Serum, J. Clin. Endocrinol. 15:215, 1955.

20. Schneider, J. J., and Horstman, P. M.: Effects of Incubating Compound E and Related Steroids with Various Surviving Rat Tissues, J. Biol. Chem. 196:629, 1952.

21. Nelson, D. H.: Determination of Adrenal Cortical Steroids in Blood, in Transactions of the Third Conference on the Adrenal Cortex, E. P. Ralli, Editor, New York, The Josiah Macy, Jr. Foundation, 1952.

22. Hellman, L.; Bradlow, H. L.; Adesman, J.; Fukushima, D. K.; Kulp, J. L., and Gallagher, T. F.: The Fate of Hydrocortisone-4-C^{14} in Man, J. Clin. Invest. 33:1106, 1954.

23. Fukushima, D. K.; Leeds, N. S.; Bradlow, H. L.; Kritchevsky, T. H.; Stoken, M. B., and Gallagher, T. F.: The Characterization of Four New Metabolites of Adrenocortical Hormones, J. Biol. Chem. 212:449, 1955.

24. Thorn, G. W., and others: Pharmacologic Aspects of Adrenocortical Steroids and ACTH in Man, New England J. Med. 248:369, 1953.

25. Silber, R. H.: Estimation of Hydrocortisone Secretion: Method of Calculation from Urinary-Excretion Data, Clin. Chem. 1:234, 1955.

26. Snedecor, G. W.: Statistical Methods Applied to Experiments in Agriculture and Biology, Edition 4, Ames, Iowa, The Collegiate Press, Inc., 1946.

27. Romanoff, E. B.; Hudson, P., and Pincus, G.: Isolation of Hydrocortisone and Corticosterone from Human Adrenal Vein Blood, J. Clin. Endocrinol. 13:1546, 1953.

28. Hudson, P. B., and Lombardo, M. E.: Analysis of Human Adrenal Vein Blood and Adrenal Glands for Steroidal Substances, J. Clin. Endocrinol. 15:324, 1955.

29. Persky, H.; Grinker, R. R., and Mirsky, I. A.: The Excretion of Hippuric Acid in Subjects with Free Anxiety, J. Clin. Invest. 29:110, 1950.

30. Eik-Nes, K.; Sandberg, A. A.; Nelson, D. H.; Tyler, F. H., and Samuels, L. T.: Changes in Plasma Levels of 17-Hydroxycorticosteroids During the Intravenous Administration of ACTH: I. A Test of Adrenocortical Capacity in the Human, J. Clin. Invest. 33:1502, 1954.

30a. Persky, H., and Heath, H.: The Effect of Intravenous ACTH on Plasma Hydrocortisone Level in Man, J. Clin. Endocrinol., to be published.

31. Sayers, G.: The Adrenal Cortex and Homeostasis, Physiol. Rev. 30:241, 1950.

32. Sydnor, K. L., and Sayers, G.: Blood and Pituitary ACTH in Intact and Adrenalectomized Rats After Stress, Endocrinology 55:621, 1254.

Delirium with Low Serum Sodium

WALTER WELTI, M.D., Seattle

Delirium immediately following surgery is a common incident and is often attributable to the anesthesia, but delirium occurring two or three days later is a puzzling psychiatric and medical problem. What has been learned about the role of electrolytes in heart disease, and more recently in surgery, now sheds valuable light on this problem.

In brief, every patient who undergoes major surgery experiences an electrolyte disturbance that may cause a psychotic or delirious reaction. Whether it does or not will depend on three factors: (1) the severity of the disturbance; (2) the treatment provided to control it, and (3) the presence of other factors which contribute to clouding of consciousness, such as sedation, hypoxia, fever, toxins, and circulatory collapse or impairment.

The clinical picture usually associated with low serum sodium and referred to as the low-salt syndrome consists primarily of weakness, anorexia, and lethargy. The patient may or may not be disoriented, delusional, or comatose. His responses may be slow and reflexes sluggish. While this description is commonly found in medical literature, case reports of central nervous system disturbance due to electrolyte imbalance are few. Saphir[1] reports 10 cases in which low sodium chloride levels were associated with psychoneurotic-like symptoms—apprehension, restlessness, loss of energy, feelings of depression, insomnia, headache, tremor, hyperreflexia, abdominal cramps, and gastrointestinal disturbances. These followed excessive salt loss by perspiration with inadequate oral intake of salt. They were treated successfully with salt by mouth over a one-week period.

Submitted for publication June 1, 1956.

From the Department of Psychiatry, with assistance from the Division of Cardiology, Department of Medicine, University of Washington School of Medicine.

Moore, writing on the low sodium syndromes of surgery,[2] reminds us that disorientation or coma may occur. He describes three basic types of low serum sodium seen in patients who have undergone surgery:

1. Low serum sodium due to severe injury or major surgery. Following trauma, sodium shifts from the serum to the body tissues, while total body sodium and body water remain normal.
2. Water intoxication or dilution of sodium, due to administration of too much water in the presence of an antidiuretic effect. This is seen in patients with chronic heart, liver, or kidney disease.
3. True sodium deficiency, as seen in dehydration when body sodium and body water are low. The serum sodium level is lowered when sodium loss exceeds the water loss, either through extrarenal routes, i. e., fistula drainage, vomiting, and diarrhea,[3] or through pathological renal loss.

Low sodium levels also occur in heart disease, as a result of vigorous use of diuretics, low-salt diet, and high fluid intake. When the sodium-depressing effects of this treatment are added to the sodium-depressing effects of major surgery, we would expect to find a greater incidence of low-sodium symptoms. Recently, the extended use of surgery in heart disease has brought more than its share of postoperative disturbances of consciousness which seem to be due to precisely this effect.

Observations

The following is a report of the various disturbances of the central nervous system seen in a survey of 27 consecutive patients following mitral commissurotomy.

Of this group of 27 patients, 9 showed neurotic-like symptoms, i. e., apprehension,

restlessness, asthenia, irritability, headache, or depression when their sodium level was at its lowest ebb. These were noted by the ward physician during routine care. The mean of the lowest serum sodium levels reached in these patients was 130 mEq/L, actually slightly higher than the mean low of the asymptomatic group. Normal serum sodium concentration ranges from 138 to 143 mEq/L.

Since these patients were subjected to many physical and emotional stresses, the neurotic-like symptoms could not clearly be attributed to the low sodium levels. All patients had been advised of the very real risk to life involved in the surgery. All experienced considerable pain, as well as total immobilization and confinement to oxygen tents. In view of this, it can only be allowed that the electrolyte imbalance present may have played a contributory role in the production of symptoms.

Of the 27 patients, 6 showed some degree of delirium, i. e., clouded consciousness, delirium, or coma. Of these, one became delirious following an alcohol infusion (serum sodium 134 mEq/L), one became comatose during a state of shock (serum sodium 130 mEq/L), and one was confused and disoriented during fever (serum sodium 131 mEq/L). Because of the presence of these other deliriogenic factors, the part played by the moderate depression of serum sodium is questionable. However, in the remaining three cases of this group, coma and delirium were felt to be clearly attributable to exceedingly low sodium levels.

These three cases were the only ones to attain levels below 121 mEq/L. They were among the first 11 patients to undergo operation. Their routine care included (1) preoperative restriction of salt to 250 mg. of sodium per day, (2) complete salt denial by mouth (no food) and by vein for two days after surgery, (3) unlimited water by mouth plus supplementary dextrose in water by vein for two days after operation. Because of the high incidence of delirium with this regime (3 out of 11 patients), the routine was changed to provide restriction of fluids just before surgery. This slight dehydration kept sodium concentrations high enough to prevent low-sodium delirium in the remaining 16 patients.

Report of Cases

The following cases illustrate the relationship of symptoms to sodium levels.

Case 1.—A 56-year-old woman was referred to the hospital for a commissurotomy after 20 years of known rheumatic heart disease. She had always considered herself a worrier, frail in physique, and nervous in temperament. On the eve of her operation she was terrified by the sudden death of the woman in the neighboring bed. However, the next morning she went to the operating room without expressing, or in any way resolving, her mounting fear of death.

The preoperative serum sodium level was 142 mEq/L after six weeks of preparation on a 250-mg. sodium diet (Fig. 1). Within 24 hours after surgery it had fallen to 128 mEq/L. The patient

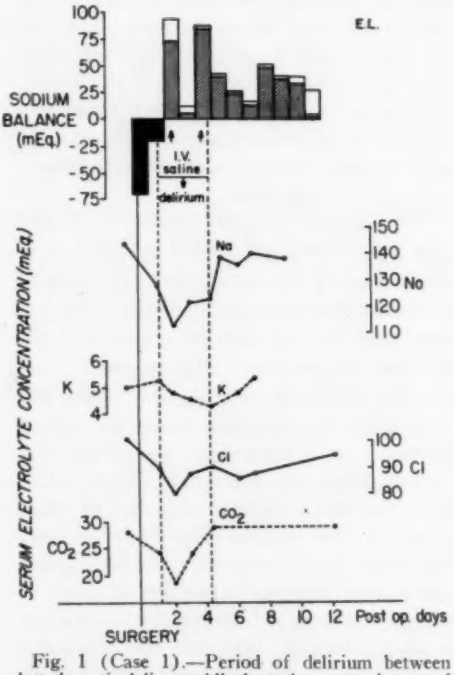


Fig. 1 (Case 1).—Period of delirium between dotted vertical lines. All electrolytes are depressed in this period. At top of figure, negative sodium balance is shown in black columns below the base line. Positive sodium balance is shown above the line. Total column height equals the sodium intake; hatched columns superimposed represent sodium loss, and the difference between the two, net salt gain, is shown in white.

was obviously anxious and complained of chest pain, but her thinking was clear and rational. On the second day confusion of thought appeared and her anxiety changed to uncontrolled panic. She prayed desperately to be spared from death and failed to recognize or heed her doctors. At the onset of her delirium her serum sodium was seen to be 113 mEq/L. Vital signs were normal. The lungs were clear, and circulation apparently adequate. She was receiving dihydromorphinone U.S.P. (Dilaudid) three times a day for pain, pentobarbital (Nembutal) at night for sleep, and her usual preoperative dose of digitoxin, as well as streptomycin and penicillin.

This very low sodium level, and the fact that intake and output records showed a positive water balance, suggested that water intoxication or low sodium was responsible for her delirium. Hypertonic (5%) saline was given intravenously over a period of five hours. This brought the serum sodium up to 122 mEq/L and produced some clearing of the delirium. For the next two days, fluids were limited to 1 liter per day, and small amounts of saline were given parenterally. As the delirium continued to clear, signs of right heart failure appeared, so that the sodium and water had to be titrated to a narrow midzone between cardiac decompensation, on one side, and delirium, on the other.

On the fourth postoperative day, the patient was responsive and alert but still disoriented (serum sodium 123 mEq/L). On the 10th day her sensorium was completely clear and the serum sodium was 135 mEq/L.

This case illustrates the abrupt decline in the serum sodium level that follows major surgery. Intake and output studies showed an uncompensated loss of about 90 mEq/L of sodium from the body in the two days following surgery (*Sodium balance,* Fig. 1). However, the serum sodium level fell from 142 to 113 mEq/L, indicating a loss of 174 mEq/L from the body's 6 liters of blood. Since only 90 mEq left the body, the remaining 85 mEq must have shifted to the body tissues.

It can briefly be stated that organic factors that embarrass cerebral function diminish the patient's internal defenses, providing an open door for irrational expression of emotion. As would be expected, the content of the delirious productions were in this case determined by the patient's personality reaction pattern and her immediate fear of death. It is not to be overlooked that all patients are greatly threatened by this dramatic and still new operation. All are advised of the real dangers before they are accepted for treatment. However, as will be seen in the following case, not all patients have as much fear or as poor methods of dealing with it, even during delirium, as the above patient.

CASE 2.—A 47-year-old placid and passive woman had been partially incapacitated with rheumatic fever and heart disease since the age of 7 years. She had had several embolic accidents, one causing hemiplagia, from which she had slight residual stiffness of her left hand. For 18 months before admission to the hospital, she was unable to do more than move slowly about the house because of symptoms of right and left heart failure.

This patient remained in the hospital three months on a measured intake of 250 mg. of sodium per day. During this preparatory period, the edema disappeared but the serum sodium remained at about 144 mEq/L until the time of surgery

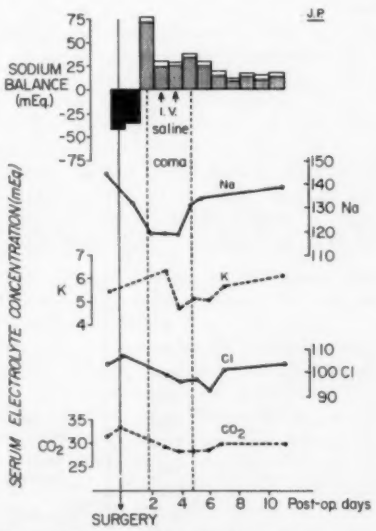


Fig. 2 (Case 2).—Period of coma between dotted vertical lines. All electrolytes are depressed during this period. At top of figure, negative balance is shown in black columns below the base line. Positive sodium balance is shown above the line. Total column height equals the sodium intake; hatched columns superimposed represent sodium loss, and the difference between the two, net salt gain, is shown in white.

(Fig. 2). The day after surgery, it fell to 131.2 mEq/L, and the second day, to 120 mEq/L. Following surgery, the patient received nothing but

water by mouth and only dextrose in water by vein for two days. Though she took in 2000 and 3000 cc. of water on these days, she lost, via chest drainage and urine, only 530 and 485 cc., respectively. Allowing for insensible water loss, she still had a positive water balance of about 3000 cc. At the same time, her sodium balance was negative, i. e., moderate loss with no replacement.

On the morning of the second postoperative day she showed no evidence of delirium or confusion on pointed examination. The serum sodium was 120 mEq/L, the temperature 99.8 F., the pulse rate 86 per minute at the wrist, the blood pressure 108/68, and respirations 16 a minute. Skin color was good. That afternoon, 45 minutes after being given dihydromorphinone hydrochloride, grain 1/32 (1.88 mg.) hypodermically (she had been receiving this amount three times a day since surgery), she became semistuporous and remained so for 12 hours. Her eyes were turned upward and were parallel. Vital signs and skin color remained good. After partial clearing, she was given dihydromorphinone HCl, grain 1/64 (0.94 mg.), and again lapsed into semistupor. For two and a half days her state of consciousness was described as "semicoma," "not responding," or "coma." No bizarre behavior, delusions, hallucinations, or emotional expression was noted by the ward physicians. The sodium level remained at 120 mEq/L in spite of a saline infusion (75 mEq/L) until the fourth postoperative day, when it rose to 130 mEq/L. On the fifth day, she regained complete consciousness, and the serum sodium level was found to be 134 mEq/L. She continued to receive dihydromorphinone, without any effect on her state of consciousness. Later in her hospital stay, she suffered an acute febrile illness, with a temperature of 103 F., but showed no further central nervous system disturbance.

Here, sedation superimposed on serum sodium depression seemed to produce a coma which was unannounced by any of the better-known symptoms of the low-salt syndrome. The coma then outlasted the action of the dihydromorphinone, clearing only when the sodium level rose to 130 mEq/L. The typical large-scale and dramatic effect of major surgical trauma in reducing serum sodium is apparent again here, and by comparison the influence of diet and diuresis seems insignificant. However, the next case demonstrates that they, too, are capable of producing delirium, with or without the help of surgery.

CASE 3.—A 27-year-old man had had rheumatic heart disease since the age of 13 and had been in the hospital many times for embolic phenomena, respiratory infections, and cardiac decompensation. He had had both right and left hemiplegia, and there was some suggestion of a residual slurring of speech. He was characterized by his family as headstrong and stubborn and had been a mild juvenile behavior problem. In January, 1950, he was hospitalized for pneumonia, and for seven days, during the febrile period, he showed confusion, disorientation, and uncooperativeness.

In December, 1950, when he was hospitalized for mitral commissurotomy, he was neither dyspneic nor cyanotic on admission. On a low-salt diet his

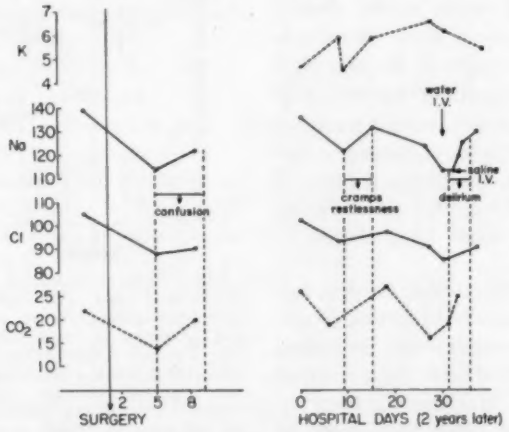


Fig. 3 (Case 3).—On the left is shown a period of confusion when sodium was depressed by surgery. On the right delirium occurred two years later, when sodium was reduced to the same low level by medical and dietary means.

serum electrolytes were in low-normal range (Fig. 3). The blood chloride level was 105mEq/L, CO_2 22 mm/L, and serum sodium, estimated from these Figures, 139 mEq/L. On the third day after his commissurotomy, he began to lose chloride by emesis. However, he remained clear in thought and cooperative in manner until the fifth day. He then complained of an inability to focus his eyes, pain in the left chest, and continued nausea. The ward physician noted, "Sensorium seems cloudy." His CO_2 level was down to 13 mm/L; the chloride was 88 mEq/L, and serum sodium, roughly 113 mEq/L. The hematocrit was 48%. The confusion and difficulty in focusing his eyes continued through the eighth postoperative day, at which time there were noted a bilateral positive Babinski reaction and a definite nystagmus on looking to the right. The CO_2 was then 20 mm/L, the chloride 90 mEq/L, and the serum sodium estimate 122 mEq/L. Two days later an eye examination showed vision to be 20/20 in the right eye and 20/30 in the left. This notation was made: "Patient has impaired word and color interpretation and appears to have some loss of accommodation. He has improved the past few days and now can name colors fairly well. I feel this is a cerebral condition and advise neurological observation. The eyes appear normal objectively."

During the period of clouded consciousness and visual complaints (5th to 10th postoperative days), the patient maintained normal blood pressure and a temperature elevation of not more than 2 degrees (F). There was no evidence of increasing circulatory or respiratory embarrassment. The BUN ranged from 10.8 to 15.0 mg. per 100 cc. He received only acetylsalicylic acid for pain and pentobarbital, 90 mg., for sleep. He was on digitalis, 100 mg., and meralluride (Mercuhydrin), 0.5 cc. daily. Because of anorexia, his liquid, no-salt diet was poorly taken. His physical condition improved steadily after this period, and no further note was made of his mental status.

The cause of the clouding of sensorium was not recognized by the physician, and no specific steps were taken to correct the electrolyte disturbance. It was only when the patient returned to the hospital in congestive failure two years later that the cause of his postoperative delirium was surmised to be low serum sodium.

At this time, failing circulation and extreme edema required that every measure be taken to reduce his serum sodium, although it was already just below normal (136.3 mEq/L). His CO_2 was 26 mm/L, chloride 102 mEq/L, potassium 4.7 mEq/L, and hematocrit 50%. By salt restriction, diuresis, and the withdrawal of salt-containing ascites fluid from the abdomen, the sodium level was reduced to 122 mEq/L by the eighth hospital day. At this point the patient became restless and began to complain of abdominal cramps. These were thought to be due to low serum sodium, but were only slightly relieved by 200 cc. of isotonic saline intravenously.

By the 30th day his serum sodium had dropped to 114.1 mEq/L. At this low level no signs of cerebral disturbance were noted for 24 hours. Then two factors were added which further distorted the electrolyte picture: (1) Vomiting began, resulting in loss of chloride and depression of serum sodium, and (2) water was given intravenously (1500 cc. of 5% dextrose in H_2O), diluting all electrolytes. While this solution was running in, the first signs of confusion appeared, with slowing of speech and thought and a markedly uncooperative attitude. The patient could not recall the names of his doctors. Serial subtractions (100—7, etc.) were slow and faulty, requiring 165 seconds and involving five errors.

A few hours later, vomiting recurred, and abdominal cramps became severe. He was given ½ grain (30 mg.) of codeine hypodermically and an hour later began complaining that the room was changing—"The door gets big and then small with each breath." The curtain around the bed "changed" to a darker blue; the colors on the facial-tissue box were changing from coral and blue to orange and green. Such a shift toward yellow in vision is sometimes associated with digitalis intoxication. However, this patient was receiving only 0.1 mg. of digitoxin daily. He felt that he was changing into someone else's body and then back into his own with each breath. "Voices sound different, but I can't explain how—they just seem different." The time of day and his location seemed to shift from moment to moment. He was baffled and slightly alarmed by these distortions in perception but was also able to consider them objectively. At this point his thinking was much slower, and after each serial subtraction he had to be brought back to the problem by the examiner. Temperature and respiratory rate were normal. The pulse showed the irregularity of auricular fibrillation but had not been accelerated. He was vomiting and dyspneic. The circulation time was doubtfully recorded at 53 seconds (arm to tongue). No increase in his degree of cardiac failure and no decrease in oxygenation could be detected during this period of hydration and delirium.

After about two hours, he began to try to fix the shifting illusions by commanding the nurses and doctors to stand still: "Don't move—don't move; don't talk." At the slightest movement in the periphery of his vision, he would shout: "You moved! You moved! Now it's gone. You'll change."

A 5% saline solution was started intravenously at a fast drip, and within 15 minutes, 50 cc. of

5% saline having been given, he remarked, "Things are the same again now." He looked about the room, approving of his visual impressions. "My hand seems small again; it seemed to get big before." When he had received 450 cc. of saline, his sodium level was 120.0 mEq/L and the potassium 4.7 mEq/L. At this point he was still slightly confused but experienced no more illusions.

The next day he appeared calm and clear and recalled his sensations of the night before. "I had a peculiar floating feeling. It made me sick when things moved. I thought I could make 'em stand still. Now everything is normal again." However, as the acute delirium cleared, a suspiciousness and open resistiveness were seen to remain. He refused to talk to certain of the ward personnel, insisted on leaving the hospital, and tried to run out in his bedclothes when his parents refused to take him home. Although his serum sodium ranged between 121 and 131 mEq/L, he became less confused but more belligerent and uncooperative, until further metabolic studies became impossible. On his 45th hospital day, he was discharged to his parents because nothing short of physical restraint could keep him in the hospital.

Three weeks later he returned to the hospital with rapidly failing circulation and respiration. During the day he was clear in thought but irritable. At night he became irrational and shouted threats that he would leave the hospital or commit suicide. The serum sodium varied from 126 to 129 mEq/L. Death due to circulatory failure occurred a week after this last admission.

This case again illustrates the dramatic and prolonged (10 days) depressing effect of surgical trauma on the serum sodium when treatment is not applied to correct it. The patient's return to the hospital two years later provided a clear demonstration that depletion of sodium alone, without the shift produced by major surgery, is capable of producing the same degree of delirium. The administration of sodium brought prompt clearing, but the sodium level could not be allowed high enough to maintain total clarity of thought without overloading the circulatory system. Treatment was gauged to avoid the extremes of both delirium and circulatory failure. The psychotic-like picture that followed the delirium and lasted until the patient died, four months later, was thought to be facilitated by his confusion, as well as by the distressing effect, of his inexorable decline. Its content and pattern, however, seemed to be determined by the predominantly headstrong and rebellious elements in his personality.

Summary and Conclusion

Reduction of sodium concentration in the blood is capable of causing delirium. This, in turn, is reversible by the administration of sodium.

Some of the mechanisms by which serum sodium is reduced are discussed, with particular attention to those encountered in major surgery and in the treatment of cardiac edema. A dangerous combination of sodium-depressing mechanisms is seen to occur when sodium-depleted cardiac patients undergo major surgery.

From a survey of 27 patients who had mitral commissurotomies, 3 cases of low-sodium delirium are reported. Symptoms began only when the serum sodium reached 121 mEq/L or lower. However, clearing occurred only when the level returned to 130 mEq/L or higher.

That delirium may also occur without major surgery was apparent in a case in which stringent deprivation and diuresis of sodium were used in the treatment of cardiac edema.

Since delirium may be the only detectable sign of sodium depression, it is suggested that a serum sodium determination be done in any undiagnosed disturbance of consciousness occurring within the first week after major surgery. Levels below 130 mEq/L would direct treatment toward careful restoration of the sodium or to dehydration to increase its concentration. An abrupt favorable response to this may be considered a confirmatory diagnostic test, although complete clearing of delirium may not occur for days. Levels above 130 mEq/L would direct attention to other possible causes of the delirium.

REFERENCES

1. Saphir, W.: Chronic Hypochloremia Simulating Psychoneurosis, J. A. M. A. 129:510-512 (Oct. 13) 1945.

2. Moore, F. D.: The Low Sodium Syndromes of Surgery, J. A. M. A. 154:379-384 (Jan. 30) 1954.

Books

Book Reviews

Aspects de la psychiatrie moderne. By Jean Delay. Price, not given. Pp. 115. Presses universitaires de France, 108 boulevard Saint-germain, Paris 6°, 1956.

In this small book the professor of psychiatry at the University of Paris has collected three addresses which he made, respectively, when he assumed the chair of psychiatry, at the opening of the First World Congress of Psychiatry, and before the 52d Congress of French-speaking neurologists and psychiatrists.

In the first two addresses Professor Delay outlines the two lines of development of psychiatry in the first half of the twentieth century—the biological and the psychological. The treatment of the subject is almost identical in the two addresses except that, in the second, he mentions the names of those who will treat of the various aspects in the sessions of the Congress. Delay develops the theme that this dualist approach is merely two aspects of the Janus-headed subject of psychiatry and that the two tend to come together in the psychosomatic approach. Nothing new is developed in these addresses, which present simply a rapid summary of developments.

The first address, however, begins with a charming French custom, which should be more widely imitated. When a French professor takes possession of a chair in his inaugural lecture, he outlines the direction which he expects to follow in his teaching and investigation and relates his orientation to the influence of his teachers. These intimate sketches of the men under whose influence his professional character was developed often recall to our memory humble workers in the field who might otherwise remain obscure or even entirely unknown to the medical world, but whose influence was entirely out of proportion to their international reputation. The international reputation of many physicians rests too often on extraneous factors, such as the profusion of their writings (and often on their obscurity, which gives a false impression of profundity) or on the influence of one or more propagandists who spread their renown abroad. If one wants to know the real value of a man, it is often to be found in just such a brief and intimate acknowledgments as are found in these inaugural lectures. This reviewer was happy to have recalled to his memory that remarkable man—Edouard Pichon—whose inexhaustible knowledge of medieval France was a source of continual astonishment. His repertory of ancient French songs made the *salle de garde* at the Salpêtrière a recreation of the true Gallic spirit, without an experience of which no man can understand France.

The last address is quite different. In it Delay attempts to answer two questions: (1) In what measure can a psychological disequilibrium favor creative activity? (2) In what measure can the latter aid in establishing a new equilibrium in the personality? After reading the fifteen pages devoted to the first question, to this reviewer the problem seems to be as mysterious as the leap from the psychic to the organic taken by a hysterical patient was to Freud. Delay tries to distinguish what he calls process from development. Process, as he uses the word, implies a rupture in the personality, which can create nothing new but can only liberate in Jackson's sense. A neurosis, on the other hand, can be creative. When one tries to analyze this part of the address, the dualism is not clear; the neurosis should be opposed by the psychosis, which the processus is supposed to cause. And here one comes up again against the strange reluctance of the French psychiatrists to use the insight of Janet, who showed long ago that a neurosis is also the result of a processus of obscure nature which lowers the psychological tension and liberates activity on a lower plane of adaptation to reality. From this point of view the neurosis appears also as a dissolution, and the psychological distinction which Delay attempts to establish between the neurosis and the psychosis disappears. The creativity which is released in the neurotic being on a lower level of adaptation to reality appeals mainly to other neurotics.

In answering the second question, the author seems to succeed better. Such literary methods of psychotherapy have been resorted to not only by poets and romancers but also by many eminent psychiatrists who succeeded in such creative activity not only in quieting their own anxieties and curing their own psychoneuroses but also in provoking similar attempts on the

part of other psychiatrists, hence the many warring sects, since much of this endeavor takes into account only a small part of psychiatric reality and is therefore on a low plane of the intellectual hierarchy, as Pierre Janet knew only too well.

This last address merits the serious consideration of psychologists. It raises very important questions and treats them with the charming eloquence of the best French tradition.

The Object Relations Technique. By Herbert Phillipson, M.A., Clinical Psychologist, Tavistock Clinic, London. Price 21s. Pp. 230. Tavistock Publishers, Ltd., 2 Beaumont St., London WI; The Free Press, Glencoe, Ill., 1955.

This work presents a statement of the basic theoretical framework developed by the British school of psychoanalysis, which emphasizes the importance of unconscious object relations in determining the subsequent perceptual world and interpersonal relationships, and a testing technique that is a logical extension of that framework into the field of psychological assessment. The theory of object relations that has been developed by Fairbairn and others, in England, has focused on the importance of unconscious object relations of a fantasy nature which were incorporated at an early stage and never relinquished and which play a vital role in determining the nature of the phenomenal world in the adult. The derivation of the testing technique from the theoretical rationale is an important step methodologically that should lead to a direct communication among the clinicians who proceed from the same framework, thus eliminating the many test-centered and esoteric conceptual systems that now pervade the field. This close relationship between technique and theory may, however, serve to limit the usefulness to those who work within the more classical analytic framework. Further exploration with the technique will be needed to evaluate these limitations. The test is an interesting one and consists of 12 cards representing ambiguous social situations, from lone figures to group constellations, as well as variations in the degree of structure and the introduction of color. One detailed case study and several briefer analyses are presented, and they provide a base line for the use of the test, as well as an interesting example of the application of the rationale on which the test is based. These studies, combined with the definitive data from a sample of 50 patients in an outpatient psychiatric clinic and 40 normal adolescent girls, suggest the wide range of material that can be expected from the technique.

Present-Day Psychology. Edited by A. A. Roback, Ph.D. Price, $12.00. Pp. 995. Philosophical Library, Inc., 15 E. 40th St., New York 16, 1955.

This symposium, an outgrowth of the editor's "History of American Psychology," presents a broad overview of psychology during the past quarter-century, purporting to treat not only the traditional areas but also areas that are inaccessible or usually neglected. Consisting of forty chapters, prepared by thirty-eight authorities, the volume is divided into five parts: topical departments, fields, dynamic and clinical psychology, methods, and psychological borderlands and humanistics. A tremendous diversity of subjects is represented. They range from general neurology, sensation, cognition, parapsychology, and animal, abnormal, educational, social, and military psychology, to psychodiagnostics, projective techniques, psychosomatics, psychotherapy, psychodrama, hypnotherapy, speech, and the psychology of literature, art, aesthetic judgments and religion, to name but half the topics included.

The editor's claim that this is perhaps the most comprehensive survey of psychology, outside of an encyclopedia, certainly appears to be justified. Yet it leaves much to be desired. The chapters are uneven in coverage and aim. Some are simply reviews or bibliographic summaries of the literature, while others present the writer's own highly specific view in a particular area of interest. Still others, unfortunately too few, deal with contemporary issues in theory and the nature and implications of differing frames of reference toward similar psychological problems. Noteworthy in this last category is Dr. Magda Arnold's superlative discussion of the present status of emotion, a most stimulating and thought-provoking article prepared at a level that would almost warrant publication in a professional journal. Although it is true that Dr. Arnold is graciously allowed at least twice as many pages as other contributors, the fact that excellent presentations are possible in the regular space allotted is demonstrated by Dr. Paul Bakan's cogent evaluation of the current approaches to perception. These essays stand in sharp

contrast to the disappointingly meager and sterile chapter on adolescence, which oversimplifies and abounds in platitudes, and to the chapter on child psychology, which is scarcely more substantial. The two chapters on methods, containing discussions of statistics and probability and an orientation termed "intergrational psychology," are so vague and general as to be of little value.

While in most instances the language is as free from technical jargon as one may reasonably expect, a startling exception is encountered in Dr. James C. Moloney's essay on body image, which, although of extremely high caliber, is written in complex psychoanalytic idiom and is difficult reading even for those fortunates familiar with the terminology.

In the light of such considerations, one cannot help wondering about the audience for whom this book is basically intended. Sad to relate, neither the editor's prefatory remarks nor this reviewer's labored efforts provide much clarification of this question.

Nevertheless, despite these limitations, there is much material that is worth while. Most of all, the reader will discover in this symposium information that simply is not available elsewhere within the confines of a single volume. The adherents of Stekel, Adler, and Sullivan, as well as those of Freud, are permitted to have their say. Subjects such as the psychology of character and attention, which present-day theorists tend to subsume under the larger rubric of personality, on the one hand, and the adaptive aspects of cognitive functioning, on the other, are here isolated for separate scrutiny. The six chapters devoted to humanistics are rather unique and interesting and point to other varieties of human endeavor with which psychologists could well be more concerned.

The Nurse and the Mental Patient: A Study in Interpersonal Relations. By Morris S. Schwartz and Emmy Lanning Shockley. Price, $3.50. Pp. 289. Russell Sage Foundation, 505 Park Ave., New York 22, 1956.

Experiencing the Patient's Day: A Manual for Psychiatric Hospital Personnel. By Robert W. Hyde, in Collaboration with the Attendants of Boston Psychopathic Hospital. Price, $2.20. Pp. 214. G. P. Putnam's Sons, 210 Madison Ave., New York 16, 1955.

Newer knowledge of group dynamics and of interpersonal relations has had a profound effect on psychiatric theory and practice. The recent interest in the population of mental hospitals by social psychologists and anthropologists has brought new life into the so-called milieu therapy for psychiatric patients in state institutions, psychiatric units in general hospitals, and sanitoria.

These two books are concerned with the practical problems involved in understanding and treating mental patients by the nurse (Schwartz and Shockley) and by the psychiatric aide or attendant (Hyde). Both authors use the same method—a frank and open discussion of the day-by-day situations that the nurse or aide encounters on the psychiatric ward. From these, certain general principles are extrapolated. Hyde makes much of the attendant's fears of the patient because of the same things he fears most in himself. Schwartz and Shockley suggest a continuous process of asking questions, getting answers, making changes, evaluating results, and again modifying procedures.

Both are good books—they contain much information for the nurse and aide, and they outline a process by which psychiatrists in their own institutions may set up a similar teaching program.

Patterns of Mothering. By Sylvia Brody, Ph.D. Price, $7.50. Pp. 446. International Universities Press, Inc., 227 W. 13th St., New York 11, 1956.

For a long time psychiatrists, and especially psychoanalysts, have been aware that the crucial period for the development of healthy and sick personalities lies in the first weeks of life and that this development is dependent upon the crucial transactions between mother and infant. Reconstructive attempts from psychiatric interviews and deep analysis of the patient's memories of the past have not sufficed to do more than focus attention on this early period. Many small studies have been reported of observations on the early mother-child relationships in the first weeks of life, but these have been sporadic and for the most part not well conceived or documented. Therefore, when Dr. Brody's book appeared, the medical profession looked forward with a great deal of anticipation to learning about her long-term careful studies of the behavior of mothers

and infants in the first period of life. Her book far surpasses expectations in the carefulness of observation, the scientific analysis of the data, and the excellently and well-written exposition of her results.

Dr. Brody has studied the behavior of thirty-two mothers of infants between 4 and 28 weeks of age. She rightfully contends that at this period the mother and infant constitute a unit of study for which direct observations are necessary to determine individual differences and general patterns. It is hypothesized that the feeding behavior is nuclear to any typology of maternal behavior. Her work is expounded in three parts: one, a method of quantitative analysis of maternal behavior; two, a typology of maternal behavior, and, three, the unique qualities that maternal feeding behavior contributes to the development of infantile personality.

The first part of the book deals with the literature on maternal behavior and considers adequately the literature on animal observation and experimentation, cultural data, and clinical data. The author points out that little is known of the processes through which maternal behavior is linked to behavior in the infant. The literature on infantile growth is thoroughly reviewed, and the question of the optimal range of stimulation and restraint of the mother in its effect on the child is raised. From an analysis of the literature on the feeding behavior of infants, the author points out that little is known concerning the effect of rhythm or activity of the infant as it calls forth maternal responses that determine what aspects of this situation save the infant from irreparable harm.

In the second part of the book, Dr. Brody describes the methods of her observations. The mother and baby are observed for four hours by three investigators in an office visit. Following this, a home visit is made to describe the environment. Then the mother fills out a questionnaire, answering the specific questions that the observers have raised. Often movies are made of the mother-child relationship. In the method and in the book are adequate descriptions of the mother and child during the observational period of thirty-two cases. Essential activities are selected for rating, and scales of maternal response according to six variables are dealt with statistically. These include feeding, cleaning, moving, touching, offering of objects, and speaking. For the purposes of typology there is a division of the subjects into four groups for all six activities, and intercorrelations are made. In order to avoid a bias in regard to the significance of these groups, they are labeled only as A, B, C, and D. In the Appendix the author presents the actual forms for case analyses and the observational records. She includes the statistical data in easily understood tables.

Each group is described in terms of maternal attitudes. The question is raised: Is feeding the independent variable by which to assess maternal behavior? The answer is "yes" from twenty-two of twenty-four mothers of infants of 12, 20, and 28 weeks of age. The answer is "no" for eight infants 4 weeks of age and two older infants. For each group the feeding behavior of the mother is carefully described.

In discussing the uniqueness of the maternal responses, the author states that the response of the mother to the instinctual needs of the infant in any phase of his psychic development spreads and governs her general responses to the infant. There seems to be some correlation between infant development and maternal behavior, but it does not assume causal significance. The influence of the infant's activity on the mother does not seem as significant as the mother's feeding technique which is more related to her own personality and attitudes and experience than to the infant's age and activity level. The author tends to minimize the influence of the child on the mother. The child's ego functions emerge not only because of maturation of inborn structures but also because of an identification and imitation of maternal behavior.

Dr. Brody then goes on to attempt to correlate maternal behavior with the mother's method of dealing with her beating fantasies. These fantasies are defenses against her past active incestual wishes toward her father. If considerable masochism remains, the mother subjugates her own ego to that of the child and indulges and overprotects him. If there is a struggle against the masochistic wishes, there results an anxious mother who fears doing too much for her child. If the mother represses her masochistic impulses, she has a tendency to be more equal with the child and does not worry about him or make too many demands on him.

If the mother has developed a reaction formation against her masochistic impulses,

she attempts to take the active role of the father and become dictatorial and controlling. If the mother identifies with the aggressor in dealing with her beating fantasies, she becomes sadistic toward the child.

It is in this last aspect of the work that the author takes off into the use of psychoanalytic theory in an attempt to describe the formation of the specific and unique maternal behaviors. Here her argument is weakest because she does not have objective material to document her hypotheses. Nevertheless, she has the privilege of suggesting that this area of uniqueness of maternal personality can be tested and correlated with maternal behavior toward young infants. Aside from this last section, the book is an exquisite example of an objective and scientific and well-controlled series of observations in an area of great significance for the science of psychiatry. There are an excellent bibliography and an adequate index. The book is a fascinating document and most interesting to read and is recommended for all persons in the various disciplines concerned with human behavior.

Culture, Psychiatry and Human Values. By Marvin Kaufmann Opler. Price $6. Pp. 260. Springfield, Ill., Charles C Thomas, Publisher, 1956.

Opler's book "Culture, Psychiatry and Human Values" is an important milestone in the growth and development of the field of social psychiatry. Indeed, an alternative title for the book would be "Principles of Social Psychiatry." Students in this area (psychiatrists, psychologists, social workers, nurses, etc.) will find an excellent review of relevant topics, ranging from the implications of cultural and subcultural relativity upon psychiatric theory to the therapeutic significance of the social structure of a psychiatric hospital. The bibliography will be especially useful for psychiatrists, in that it brings together pertinent material from a wide variety of sources, including many significant papers outside the range of those most commonly quoted in psychiatric journals.

The book contains lucid documentation of studies which illustrate inadequacies of many psychiatric beliefs. For example, attention is called to Roth and Luton's investigation in Tennessee which revealed that rural communities had high rates of mental incapacitation. Another example involves the oversimplified belief of "complexity" of modern culture as a primary cause of current problems. Although the stereotype of Rousseau's primitive man leading the happy and simple life has been abandoned by anthropologists, it remains quite alive in psychiatric circles.

Throughout the book there is evidence of thoughtful consideration and practical understanding of problem areas in psychiatry and psychoanalysis. Opler is deeply committed to developing methods which will aid in the integration of the epidemiological and clinical approaches. At one point he states, "Put differently, neither the psychogenetic nor the epidemiological approaches meet the requirements of etiological knowledge when used singly. When used together, the first to provide a rounded verification of psychiatrically valid hypotheses, and the second to test statistically the hypotheses concerning groups of people, the combined methods of research may yield the kind of data which withdraws support from competing explanations and really withstands rigorous scrutiny." This delineates a basic purpose for the book.

Two groups draw the major share of the author's criticism. Perhaps Opler most sharply disagrees with Mead, Benedict, and LaBarre when they focus on "cultural psychopathology." Repeatedly the point is made that such analogizing between clinic and culture is much too gross and omits crucial nuances. Opler is also critical of psychoanalytical theory, saying, "While vast insights were developed in the Freudian movement, and in other psychiatric theories, the drive in the former movement towards a unitary theory of pan-human psychic development was premature. The universal theory did not adequately account for variations in human behavior across cultural lines, or between different disease processes, or even within a range of symbolic mechanisms of interpersonal communication. It had little to say about positive aspects of culture in interpersonal relations for creative and productive purposes." At another point he states that the epiphenomenal view of culture, as illustrated by Freud's "Totem and Taboo," has shattered "against the hard facts of cultural relativity." Similarly, he points out the limitations of Lowie and Malinowski when they exclusively ascribe a biological-need basis to culture.

While making an independent synthesis of his own field of anthropology with social psychology, psychiatry, and psychoanalysis, Opler shows a definite bias toward certain ideologies and groups of psychiatrists. These include Sullivan, Fromm-Reichman, Fromm, Thompson, and Horney, in addition to his colleagues at Cornell, Rennie and and Diethelm. The extent of the bias seems to reflect one weakness in the synthesis that emerges. It appeared to the reviewer that the book lacked depth in its handling of biological systems, varying from the omission of psychosomatic and physiological literature relevant to its thesis to a de-emphasis of genetic, constitutional, and maturational factors that are relatively unaffected by cultural variation. Opler is optimistic about ultilizing his theoretical model in a multidisciplinary study. In the stress of actually converting such broad experimental designs into practice, however, many projects begin to reduce toward a hard core of basic beliefs. It is at that point that structural weaknesses of the design and biases clearly emerge. Of course, the test of Opler's synthesis will involve its usefulness in investigating current hypotheses and developing new ones. It is certainly too much to expect at this time that an all-embracing theory of social psychiatry can be formulated. Any current design must have many weaknesses. Opler has provided us with a general model, which is being applied already by the Cornell group. The findings in that multidisciplinary study involving a large urban population in New York City should provide positive feed-back to other groups interested in social psychiatry, as well as to Opler and his colleagues.

Outside of a tendency to be slightly repetitious when citing information about references previously discussed, the author has presented a well-written, readable book. It can be highly recommended as an excellent current summation of social psychiatry.

All of
these articles have
appeared in TODAY'S HEALTH
and are now available
in one pamphlet.

ALCOHOLISM

an
important
problem
in today's living

ALCOHOLICS ANONYMOUS

Written from the standpoint of a member, the basic treatment procedures are described and the psychological problems confronting the alcoholic are discussed.

ALCOHOL AND CIRRHOSIS OF THE LIVER

Relationship between alcohol, diet and cirrhosis. Increasing stress on nutritional differences.
by Russell S. Boles

HOW TO HELP A PROBLEM DRINKER

Understanding the alcoholic's capabilities, the necessity of help, causes of his condition.
by Edward A. Strecker and Francis T. Chambers, Jr.

THE TREATMENT OF ALCOHOLISM

Tracing the steps from convincing the alcoholic that he is sick through treatment and cure.
by Lewis Inman Sharp

CONDITIONED REFLEX TREATMENT OF CHRONIC ALCOHOLISM

Its place among methods of treatment today, its development and correlation with personality factors.
by Walter L. Voegtlin

INSTITUTIONAL FACILITIES FOR THE TREATMENT OF ALCOHOLISM

Comparative differences, in drinking, with the last century, new establishments and methods of treatment, lack of trained personnel.
by E. H. L. Corwin

THE ABOVE SIX PAMPHLETS ARE AVAILABLE IN BOOKLET FORM FOR ONLY 50 CENTS

HOW EXPERTS MEASURE DRUNKENNESS

A partial transcript of an actual courtroom case.
H. A. Heise
8 pages, 15 cents

BARBITURATES, BOOZE AND OBITUARIES

A discussion of the dangers of mixing alcohol and barbiturates.
Donald A. Dukelow
4 pages, 10 cents

ADDRESS REQUESTS TO:

ORDER DEPARTMENT
AMERICAN MEDICAL ASSOCIATION
535 NORTH DEARBORN STREET
CHICAGO 10, ILLINOIS

when the patient's anxiety is complicated by depression . . .

both symptoms often respond to

THORA-DEX*

(a combination of Thorazine† and Dexedrine‡)

'Thora-Dex' is a combination of a specific anti-anxiety agent, 'Thorazine', and a standard antidepressant, 'Dexedrine'. The preparation is of unusual value in mental and emotional disturbances and in somatic conditions complicated by emotional stress—especially when depression occurs together with anxiety, agitation or apprehension.

The patient treated with 'Thora-Dex' is generally both calm and alert . . . with normal interest, activity and capacity for work.

Smith, Kline & French Laboratories, Philadelphia

'Thora-Dex' Tablets are available in two strengths:

10 mg. 'Thorazine'	25 mg. 'Thorazine'
2 mg. 'Dexedrine'	5 mg. 'Dexedrine'

'Thora-Dex' should be administered discriminately and, before prescribing, the physician should be fully conversant with the available literature.

*Trademark †T.M. Reg. U.S. Pat. Off. for chlorpromazine, S.K.F.

‡T.M. Reg. U.S. Pat. Off. for dextro-amphetamine sulfate, S.K.F.

THORAZINE*

helps to keep more patients out of mental hospitals

With 'Thorazine' "more patients will be released after shorter periods of hospitalization and fewer patients will require re-hospitalization. More patients can be treated in the community, at clinics or in the psychiatrist's office without being hospitalized at all."[1]

'Thorazine' should be administered discriminately; and, before prescribing, the physician should be fully conversant with the available literature.

For information write: *Smith, Kline & French Laboratories, 1530 Spring Garden Street, Phila. 1*

1. Hoffman, J.L.: in Chlorpromazine and Mental Health, Philadelphia, Lea & Febiger, 1955.

*T.M. Reg. U.S. Pat. Off. for chlorpromazine, S.K.F.